VOLUME 60 NUMBER 1

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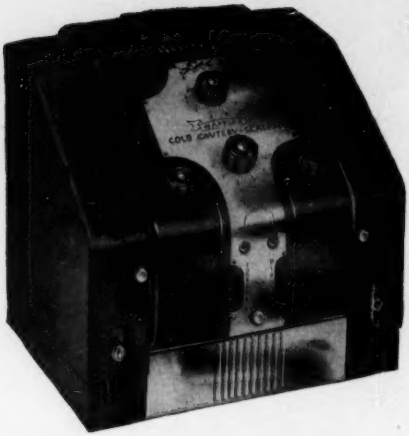

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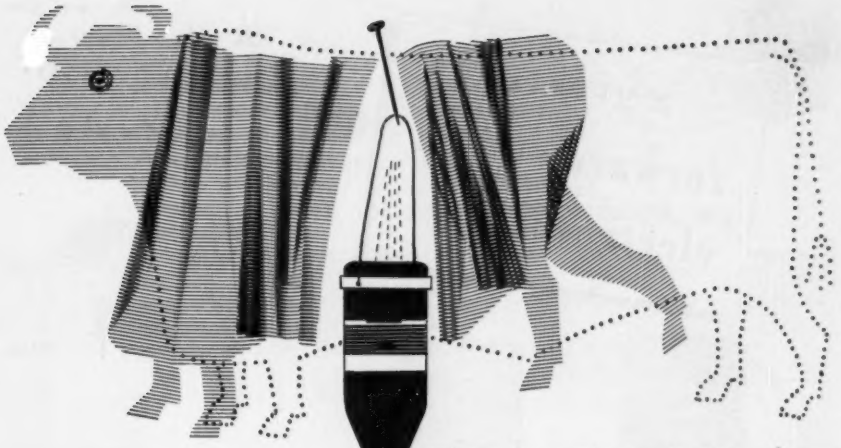

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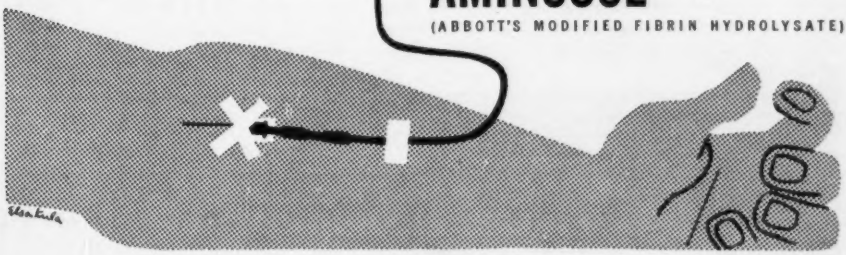

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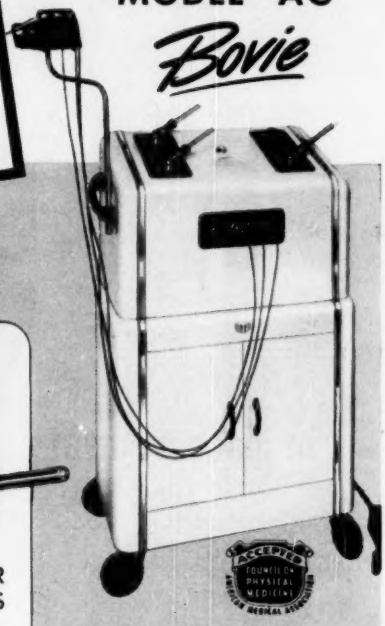

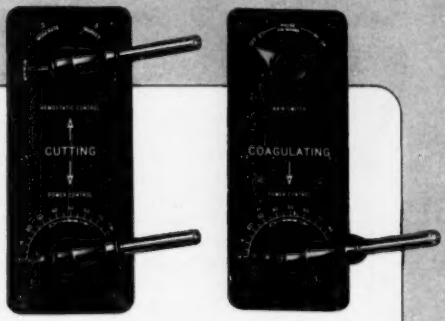

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SECRETORY STUDIES ON THE ISOLATED STOMACH

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CHICAGO

ONE OF the obstacles encountered in a study of the physiology of gastric secretion is the difficulty of subjecting the normal stomach to the physiologic stimulus of food and making a quantitative collection of the gastric secretory output. In an attempt to simplify and control the many factors present, recourse has been made to various types of gastric pouches, fistulas and other preparations made with aseptic precautions in anesthetized animals. In most cases these preparations have proved compatible with survival in good health and with relative freedom from discomfort. Our present understanding of the mechanism of gastric secretion is largely dependent on these facts. Beaumont was the real pioneer in recognizing and utilizing surgical intervention as a method for the study of gastric physiology. The gastric fistula method in man used by him was subsequently employed with great advantage by Carlson [1] and, more recently, by Wolf and Wolff.[2] In 1878 R. Heidenhain prepared an isolated pouch of the fundic portion of the stomach, and in 1894 Pavlov introduced his well known method for making a pouch of the fundus with preservation of its vagal nerve supply. It is a curious fact, to which attention was called by Jemerin and Hollander [3]

From the Department of Surgery of the University of Chicago.

This work has been aided by grants from the Committee on Research and Fellowships of the United States Public Health Service, from the Otho S. A. Sprague Memorial Institute and from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Carlson, A. J.: Am. J. Physiol. **31**:151, 1912.

2. Wolf, S., and Wolff, H. G.: Human Gastric Function, New York, Oxford University Press, 1943.

3. Jemerin, E. E., and Hollander, F.: Proc. Soc. Exper. Biol. & Med. **38**:139, 1938.

and Cope and his associates,[4] that in his description of the fundic pouch, Pavlov provided an entirely erroneous diagram of the vagus nerve supply to the stomach. The right or posterior vagus nerve does not, as Pavlov apparently supposed, supply the greater curvature of the stomach but instead is distributed along the lesser curvature in somewhat similar fashion to that of the left or anterior nerve. As a consequence, the accessory stomach pouch as described by Pavlov (fig. 1) does not contain the vagus innervation that his diagrams would lead one to suppose. Preservation of even a small portion of the vagal nerve supply to the isolated pouch is accomplished only by great care in the preparation of the isthmus, since the line of incision extends transversely across the vagus fibers and not parallel with them (fig. 2). It will, however, become evident that secretory effects resulting from the stimulation of the vagus nerve supply to the stomach do not bear a quantitative relationship to the proportion of nerves that are preserved. Preservation

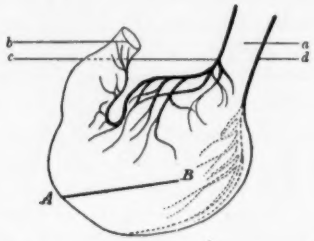

Fig. 1.—Distribution of the vagus nerves to the stomach in the dog and the line of incision for the production of the Pavlov pouch, according to Pavlov, 1910. (*a*) Esophagus; (*b*) pylorus; (*c*) left vagus nerve; (*d*) right vagus nerve. *A-B*, line of incision for Pavlov pouch.

of a small portion of the vagal nerve supply may suffice for almost a maximal physiologic response.

Modifications of the Pavlov pouch designed to secure a better vagal innervation of the isolated stomach have been prepared by Hollander and Jemerin [5] and by Cope, MacMahon, Hagströmer and Thompson.[4] The former made an effort to secure a wider isthmus to the pouch than the one illustrated by Pavlov, while the latter described a technic which preserves a large portion of the anterior vagus nerve as innervation for

4. Cope, O.; MacMahon, C. E.; Hagströmer, A., and Thompson, R. H.: Gastric Secretion: New Gastric Pouch with Nonleaking Stoma and Intact Nerve Supply; Description of Two Stage Technic Used on Dog, Arch. Surg. **40**:717 (April) 1940.

5. Hollander, F., and Jemerin, E. E.: Proc. Soc. Exper. Biol. & Med. **39**:87, 1938.

the pouch. In 1895 Fremont [6] described the totally isolated stomach in dogs with the vagus nerves divided and with the vagus nerves preserved. He stated that when the esophagus is united to the duodenum the animals continue to eat and to secrete an extremely acid digestive juice from the isolated stomach. The same stomach secretes a neutral, nondigestive fluid if the vagi are cut along the cardia. One can then obtain two kinds of isolated stomachs: one that secretes an acid digestive juice and one that secretes a mucous substance. Although the totally isolated stomach is frequently spoken of as a Fremont pouch, it is questionable from Fremont's description whether he actually secured a good preparation. Many workers have prepared the totally isolated stomach with the vagus nerves cut and have almost invariably reported a highly acid gastric secretion from the isolated stomach. In view of this fact, it is difficult

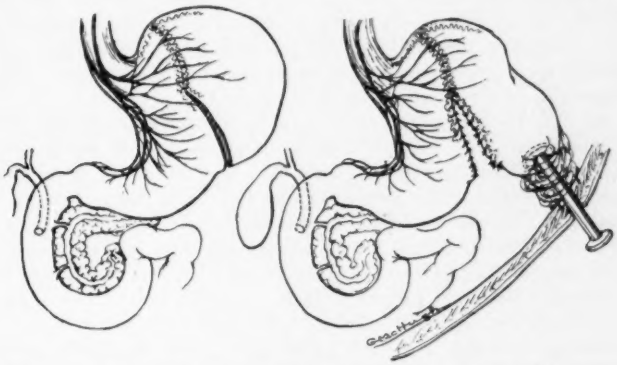

Fig. 2.—Distribution of both vagus nerves to the lesser curvature of the stomach and the paucity of vagus innervation of the Pavlov pouch even when a wide isthmus is made. Note that the line of incision for the production of the mucous membrane septum crosses the vagus fibers and that consequently these can be easily damaged.

to reconcile Fremont's statement that such a stomach secretes a neutral nondigestive fluid with the conclusion that he made such preparations. To our knowledge, Lim, Ivy and McCarthy in 1925 [7] were actually the first to make extensive use of the totally isolated stomach in dogs for the study of various problems in gastric physiology. In their preparations the vagus supply to the stomach was divided, and it seems likely that this fact accounts for the differences reported from Ivy's laboratory and the findings in this laboratory, where for the most part an isolated stomach with vagus nerves intact has been utilized. In 1930 Dragstedt

6. Fremont: Bull. de l'acad. de med. **34**:509, 1895.

7. Lim, R. K. S.; Ivy, A. C., and McCarthy, J. E.: Quart. J. Exper. Physiol. **15**:13, 1925.

and Ellis [8] described a method for preparing the totally isolated stomach of dogs with preservation of the vagus nerve supply. The animals were found to secrete from 1,000 to 2,600 cc. of gastric juice in a twenty-four hour period, and, as a result, progressive hypochloremia, alkalosis, dehydration, decrease in urinary secretion and azotemia developed. Death usually resulted in from five to eight days, but it could be prevented and the animals maintained in good condition, with the chemical structure of the blood nearly normal, for many months by the daily intravenous administration of 2,000 to 3,000 cc. of Ringer's solution. As a result of these studies, Dragstedt and Ellis concluded that the total loss of gastric juice from the body has a fatal effect and that the gastric mucosa has the capacity to separate chloride from the blood plasma and to continue that separation until the level of blood chloride is reduced to from one half to one third of the normal value and the chemical structure of the blood has become so abnormal that life cannot exist. This conclusion suggests that the mechanism for providing gastric secretion takes precedence over the mechanism for conserving the normal composition of the blood on which life depends.

In 1932 Webster and Armour [9] reported a somewhat different type of experiment and concluded that the large volumes of gastric juice reported by Dragstedt and Ellis must have been due partly to the presence of a nervous phase before the anorexia developed and partly to some other abnormal condition. In Webster and Armour's experiments, which were performed on 2 dogs, an esophagotomy was made and a silver cannula inserted into the stomach and a second cannula into the duodenum between the pancreatic ducts. After the fistulas were healed, the stomach was separated from the duodenum at the pyloric ring and the stumps inverted. With this preparation, it was possible to collect gastric secretion from the stomach and to feed the animals by introducing food into the duodenum through the duodenal fistula. Animals prepared in this fashion secreted from 270 to 560 cc. of gastric juice, which is in sharp contrast to the 1,000 to 2,000 cc. of gastric secretion reported by Dragstedt and Ellis in their experiments. Since the vagus fibers to the stomach were present in both cases, Webster and Armour concluded that some abnormal factors must have been present in the experiments of Dragstedt and Ellis.

Ivy and Grossman,[10] with a similar type of preparation, have confirmed the findings of Webster and Armour and have suggested that the large amounts of secretion reported by Dragstedt and Ellis might be due to constant irritation of the vagus nerves by scar tissue or mechanical traction.

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8. Dragstedt, L. R., and Ellis, J. C.: Am. J. Physiol. **93**:407, 1930.
9. Webster, D. R., and Armour, J. C.: Tr. Roy. Soc. Canada **5**:109, 1932.
10. Ivy, A. C., and Grossman, M. I.: Personal communication to the authors.

Two deficiencies exist in the type of preparation used by Webster and Armour and by Ivy and Grossman which undoubtedly account in part for the small volumes of secretion observed. As noted by Webster and Armour, animals prepared in this way soon lose all interest in food and refuse to eat. As a consequence, although the vagus nerves to the stomach are intact, they are not stimulated and the nervous phase of secretion is entirely absent. Furthermore, when food is introduced into the duodenum it stimulates only the intestinal phase of gastric secretion since the pylorus is closed. Recent experiments in this laboratory [11] have proved conclusively the importance of the gastric antrum in the chemical phase of secretion and the marked reduction in secretion which occurs when the antrum is removed or fails to come into contact with food.

Ivy [10] has repeatedly stated that dogs with a totally isolated stomach will not secrete themselves to death, and his claim would seem to be borne out by the fact that the dogs prepared in Webster and Armour's experiment survived for a considerable period even though none of the gastric juice entered the intestine where it could be reabsorbed.

Important data bearing on this problem have come from experiments on the pathogenesis of acute intestinal obstruction. Complete obstruction at the pylorus causes death in a few days with progressive hypochloremia and alkalosis.[12] This is attributable to the continued secretion and failure of reabsorption of the hydrochloric acid of the gastric juice and occurs even without the stimulus of food taking. These findings, repeatedly confirmed in clinical patients as well as in laboratory animals, support the conclusion of Dragstedt and Ellis that the empty stomach will continue manufacturing gastric juice until death is produced. In the intervening years, considerable experience has accumulated in this laboratory as a result of gastric secretion studies on dogs with vagally innervated, totally isolated stomach preparations as well as other types, and it seems now possible to examine the divergent results of investigators using different methods and to account for some of the differences of opinion.

EXPERIMENTAL METHODS

Four types of totally isolated stomach preparations in dogs have been utilized in this laboratory for the study of the physiology of gastric secretion. These are: (1) total isolation of the stomach with preservation of its blood and vagus nerve supply and direct end to end anastomosis between the terminal end of the esophagus and the first portion of the duodenum (fig. 3); (2) total isolation of the stomach with preservation of its blood and vagal nerve supply and end to side anastomosis

11. Woodward, E. R.; Bigelow, R. R., and Dragstedt, L. R.: Proc. Soc. Exper. Biol. & Med. **68**:473, 1948.

12. MacCallum, W. G.; Lintz, J.; Vermilge, T. H.; Leggett, T. H., and Boas, E.: Bull. Johns Hopkins Hosp. **31**:1, 1920. Haden, R. L., and Orr, T. G.: J. Exper. Med. **37**:365, 1923. Gamble, J. L. and Ross, S. G.: J. Clin. Investigation **1**:403, 1925.

between the terminal end of the esophagus and the side of the first portion of jejunum (fig. 4); (3) total isolation of the fundus and body of the stomach with preservation of its blood and vagal nerve supply and end to end anastomosis between the lower end of the esophagus and the antrum of the stomach, which is left attached to the duodenum (fig. 5); (4) preparation of a similar isolated stomach with preservation of gastric blood supply but with division of the vagus nerves.

Surgical Technic.—The anatomic arrangement of the vagus nerves at the lower end of the esophagus and the distribution of the blood supply to the upper part of the stomach are such that it seems advisable to describe briefly the technical procedure which has made it possible for us to isolate the stomach from continuity with the alimentary tract and still preserve almost its entire vagus nerve supply as well as its blood vessels. Female dogs weighing from 12 to 15 Kg. are usually

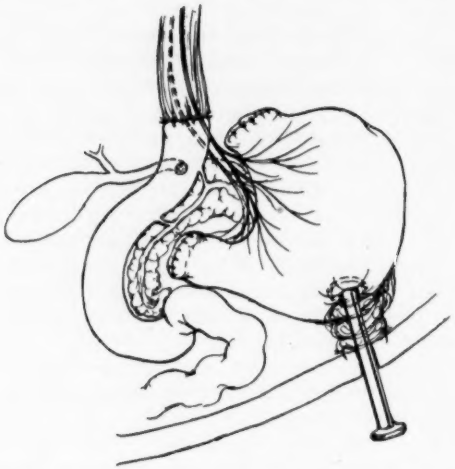

Fig. 3.—Total isolation of the stomach with preservation of blood and vagus nerve supply and reconstruction of the alimentary tract by anastomosis of the esophagus with the duodenum. Note that a generous amount of omentum is wrapped around the cannula before it is led through a stab wound in the abdominal wall.

selected, but if these are not available, males will serve equally well. The animals are fasted for twenty-four hours and anesthetized with ether. A long midline incision is made in the upper part of the abdomen and the stomach exposed. The suspensory ligament of the pylorus is divided. The spleen and omentum are delivered from the peritoneal cavity, and downward traction is made on the upper half of the stomach. The liver is retracted to the right and held in place with a gauze pack. A small opening is made in the omentum along the greater curvature of the stomach as close to the esophagus as possible. The index finger of the surgeon is inserted through this opening and passes posteriorly along the lower portion of the esophagus toward the right, or the lesser curvature. In this maneu-

ver, the esophagus is rotated in a counterclockwise direction so that the finger of the surgeon is insinuated between the vagus branches and the wall of the esophagus until all nerve branches and blood vessels have been pushed aside. In this maneuver, a blunt hook is sometimes serviceable. After the lower portion of the esophagus

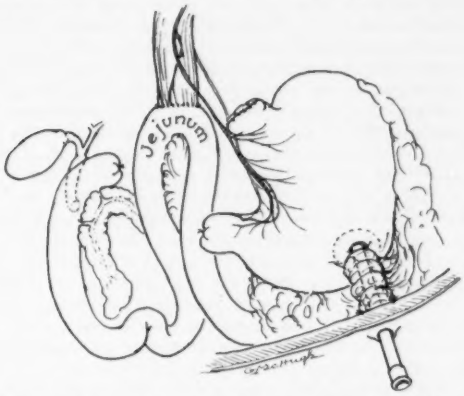

Fig. 4.—Total isolation of the stomach, with preservation of blood and vagus nerve supply and reconstruction by anastomosis of the esophagus with the side of the first portion of the jejunum.

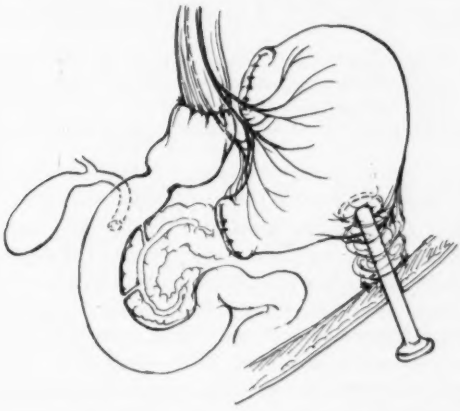

Fig. 5.—Isolation of the fundus of the stomach, with preservation of blood and vagus nerve supply and reconstruction by anastomosis of the esophagus and the antrum of the stomach.

and the upper end of the stomach have been encircled by the surgeon's finger, the vessels and nerves are further displaced by gentle upward and downward traction.

A right-angled clamp covered with protecting rubber is then placed on the esophagus and a second similar clamp on the upper end of the stomach. The lower portion of the esophagus is transected between these two clamps, care being taken not to damage the vagus nerve supply along the lesser curvature of the stomach. If the antrum is to be preserved in continuity with the esophagus, the stomach is now transected about 3 inches (7.6 cm.) proximal to the pylorus and the upper and lower end of the stomach infolded and closed. A special plastic or gold-plated brass cannula is introduced into the stomach on the anterior wall near the greater curvature and the gastric wall infolded around the cannula by two purse-string sutures. The antrum of the stomach is now anastomosed to the lower end of the esophagus by end to end sutures. The antrum may be left with the isolated fundus, in which case the lower end of the esophagus is anastomosed either to the open end of the duodenum by end to end suture or implanted into the side of the first portion of the jejunum by end to side anastomosis. In some cases it may be difficult to unite the lower end of the esophagus with the open end of the duodenum because of the small size of the latter. In these the open end of the duodenum may be closed and an end to side anastomosis made between the lower end of the esophagus and the side of the first portion of the duodenum, about 1 cm. distal to the pylorus. The cannula employed for the gastric fistula is similar to that described in 1933.[13] It may be made of lucite,® nylon® or brass coated with gold. To facilitate the passage of the cannula through the abdominal wall and to secure a tight fistula, a sharply pointed cap may be screwed to the distal end of the cannula. This is, of course, immediately replaced by the blunt cap or the rubber tube adapter for the collection of gastric juice. After the operation, a small blood transfusion is usually given, and penicillin is administered parenterally for the first forty-eight hours. Daily intravenous injections of sodium chloride solution are given in amounts ranging from 700 to 1,500 cc. Liquid food is usually started on the fifth day, followed shortly by semisolids and then the ordinary food of the laboratory.

The first totally isolated stomach with intact blood and vagus nerve supply was constructed in this laboratory in 1929, and in the intervening years thirty-eight such preparations have been made and studied. It is the purpose of this paper to describe some of the observations made with this type of preparation.

VOLUME OF GASTRIC JUICE SECRETED BY THE TOTALLY ISOLATED STOMACH WITH VAGUS INNERVATION INTACT

Data with respect to the amount of gastric juice secreted by the totally isolated stomach are summarized in tables 1, 2 and 3. Attention should be called to the fact that 282 accurate collections of the twenty-four hour gastric secretion were made in 1 animal and 261, 120, 87 and 81 in others. Quantitative collections were made possible by the fact that the cannula was snugly fitted in the stomach by inverted purse string sutures and wrapped with omentum before being passed through a stab wound in the abdominal wall. A rubber balloon was attached to the cannula and supported in a canvas apron worn by the animal at all times. This prevented loss of the juice through spilling.

13. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Surg., Gynec. & Obst. **56**:799, 1933.

The importance of repeated collections in a single animal is emphasized by the marked variations that occur from day to day. Thus 1 dog (table 3) secreted the astounding total of 3,245 cc. of gastric juice

TABLE 1.—*Gastric Secretion in Total Pouch Dogs with Vagus Innervation Intact (Type I. Esophagus United to the Duodenum)*

Dog No.	Date of Operation	No. of 24 Hour Collections	Volume of Gastric Juice in 24 Hours			Weight, Kg.	Average 24 Hour Secretion per Kilogram of Body Weight, Cc.
			Maximum, Cc.	Minimum, Cc.	Average, Cc.		
1-A	9/28/1928	69	1,365	128	486	16.0	30.4
465	9/23/1932	30	854	344	528	9.5	55.6
671	10/ 2/1934	87	1,041	407	594	18.6	32.0
780	9/ 8/1937	120	1,790	250	625	....	....
D-865	1/10/1947	10	1,240	525	908	14.6	61.7
D-875	2/ 3/1947	17	1,005	470	756	15.4	49.0
D-898	4/18/1947	25	650	250	415	11.8	35.1
D-912	6/ 2/1947	30	500	205	331	16.2	20.4
D-954	11/21/1947	20	730	120	453	10.0	45.3
D-962	1/20/1948	81	865	225	426	14.2	30.8
D-943	10/20/1948	17	670	330	522	10.6	49.2
Average			973	296	550	....	40.8

TABLE 2.—*Gastric Secretion in Total Pouch Dogs with Vagus Innervation Intact (Type II. Esophagus United to the Jejunum)*

Dog No.	Date of Operation	No. of 24 Hour Collections	Volume of Gastric Juice in 24 Hours			Weight, Kg.	Average 24 Hour Secretion per Kilogram of Body Weight, Cc.
			Maximum, Cc.	Minimum, Cc.	Average, Cc.		
D-802	5/27/1946	19	1,617	630	1,084	13.2	82.0
D-804	6/14/1946	4	540	430	491	10.8	45.5
D-806	7/15/1946	25	805	140	451	10.8	41.7
D-812	9/10/1946	10	1,042	580	802	13.7	58.6
D-835	10/23/1946	37	440	65	201*	12.4	21.1
D-839	11/ 1/1946	21	1,190	345	662	12.2	54.4
D-861	12/31/1946	7	710	450	604	11.2	53.8
Average			906	377	622	....	51.2

* There was repeated failure to secure a secretory response to insulin hypoglycemia. The vagi were intact at autopsy.

during one twenty-four hour period and only 260 cc. during another. Similar variations, though not so marked, were encountered in all the animals. Certain factors that appear to produce these variations will be discussed later.

The data are grouped in three tables depending on slight but nevertheless important modifications in the method employed for reconstruc-

tion of the alimentary tract after the isolation of the stomach. Thus in table 1, covering the operation in which the entire stomach was isolated and the lower end of the esophagus united to the open end of the duodenum (fig. 3), the average maximum secretion in each twenty-four hour period is 973 cc., with a minimum of 296 cc. and an average of 550 cc. In table 2, recording an operation in which, after a similar isolation of the entire stomach, the lower end of the esophagus was sutured to the side of the jejunum (fig. 4), the average maximum secretion in each twenty-four hour period is 906 cc., the minimum 377 cc. and the average 632 cc. When the antrum was not included with the isolated stomach but was left attached to the duodenum and sutured to the open end of

TABLE 3.—*Gastric Secretion in Fundus Pouch Dogs with Vagus Innervation Intact (Type III. Esophagus United to Gastric Antrum)*

Dog No.	Date of Operation	No. of 24 Hour Collections	Volume of Gastric Juice in 24 Hours			Weight, Kg.	Average 24 Hour Secretion per Kilogram of Body Weight, Cc.
			Maximum, Cc.	Minimum, Cc.	Average, Cc.		
682	2/19/1929	35	2,660	350	1,271	16.3	78.0
2,813	5/23/1929	13	1,470	180	1,025	17.8	57.0
740	1/19/1932	261	1,635	500	1,143	14.4	63.9
877	3/22/1933	63	1,400	32	662	13.1	50.5
109	11/22/1933	10	1,490	1,230	1,360	15.2	....
312	3/ 5/1934	19	1,194	200	618	11.3	54.6
6	4/26/1935	6	1,446	462	1,041	21.0	49.5
672	8/ 2/1937	282	3,245	260	1,065	....	....
996	7/ 8/1948	45	1,200	200	625	13.0	48.1
D-16	8/24/1948	24	1,080	360	697	13.2	52.0
Average			1,687	377	950	....	56.7

the esophagus (fig. 5), the average maximum secretion in each twenty-four hour period was 1,687 cc., with a minimum of 377 cc. and an average of 950 cc. (table 3).

It is thus evident that when the secretory portion of the stomach is totally isolated and its blood and vagus nerve supply preserved, most gastric juice is secreted when the reconstruction of the alimentary tract is arranged, as in figure 5, so that the food must come in contact with the gastric antrum and least is secreted when the food passes directly from the esophagus into the jejunum, as in figure 4.

These findings are in harmony with the concept that the antrum of the stomach plays a special role in gastric secretion, perhaps in the manner postulated by Edkins.[14] It is evident that preservation of the gastric antrum as a part of the isolated stomach where it does not come

14. Edkins, J. S.: J. Physiol. **34**:133, 1906.

in contact with food does not bring about the large volume of gastric secretion observed when the antrum remains a functional part of the alimentary tract. Even a small portion of antrum so remaining may suffice to stimulate gastric secretion. This is undoubtedly in part the explanation for the large volume of gastric secretion from the vagally innervated isolated stomach reported by Dragstedt and Ellis.[6] In the early experiments, not infrequently a small cuff of gastric antrum was left attached to the duodenum and united to the open end of the esophagus. Mention was not made of this fact because at that time the mucosa of the antrum was not considered to be of greater significance than that of the duodenum or jejunum.

Criticism has sometimes been directed toward our practice of fitting a cannula snugly into the isolated stomach or Pavlov pouch on the basis that the constant presence of such a foreign body might of itself stimulate gastric secretion and so vitiate the results secured. There is little or no basis for this concern. Mechanical stimulation without distention has not been found to stimulate acid secretion in the stomach. On the other hand, the snugly fitted cannula makes possible the quantitative collection of gastric juice both day and night, which is not possible with the usual type of gastrostomy. Furthermore, the complete absence of excoriation of the skin in the region of the fistula adds much to the comfort of these animals and probably on this account secures a more physiologic preparation.

FATAL EFFECT OF THE TOTAL LOSS OF GASTRIC JUICE

The conclusion of Dragstedt and Ellis [6] that the total loss of gastric juice from the body by means of the vagally innervated isolated stomach has a fatal effect has been repeatedly confirmed. In general, the survival period depends on the volume of gastric juice secreted. Animals that secrete initially a large volume of gastric secretion die much sooner than those in which the secretion is less. Death from the secretion and failure of reabsorption of gastric juice in total pouch dogs may occur at any time from six to twenty days after the construction of the total pouch. The uncomplicated effect of the loss of gastric juice is best exhibited in animals that have been preserved in good condition by the intravenous administration of isotonic sodium chloride solution for several weeks when all wounds are healed and there has been complete recovery from the surgical trauma. The cessation of intravenous injections and the withholding of salt by mouth result in progressive loss of weight, depression, loss of appetite, muscular weakness and, finally, death. These symptoms are accompanied with a progressive fall in the concentration of the blood chlorides until, in an extreme case, a concentration

which amounts to a third of the normal level may be reached. As the chlorides decrease, the carbon dioxide–combining power of the plasma increases and the p_H shifts gradually toward the alkaline side. As the secretion of urine lessens, a progressive increase in the concentration of nonprotein and urea nitrogen in the blood occurs. In the early stages of depletion, complete restoration may be secured by the intravenous administration of large volumes of isotonic sodium chloride solution. When, however, the animal has become moribund, such treatment may become ineffectual, probably owing to the development of irreversible changes. This fatal effect from the loss of gastric juice may also be seen in dogs provided with a large Pavlov pouch, which consequently may secrete initially from 1,000 to 1,500 cc. of gastric juice in a twenty-four hour period. It is thus not to be accounted for on the basis of trauma to the vagus nerves at the level of the lower end of the esophagus or of some special condition inherent in the totally isolated stomach. Such a fatal effect is not seen if the vagus nerves to the isolated stomach have been divided or if a large Heidenhain pouch is prepared.

The conclusion that the total loss of gastric juice has a fatal effect is supported by the rapid demineralization, dehydration, hypochloremia and alkalosis that occur in both man and the lower animals in the presence of gastric and high intestinal fistulas. There are thus no factors present in high intestinal obstruction and peculiar to this condition that lead to the fatal loss of water and chlorides from the body. The integrity of the vagus nerve supply to the stomach, however, seems to be essential. Thus we have repeatedly confirmed the statement of Ivy that dogs with a totally isolated stomach but with the vagi cut survive without the parenteral injection of sodium chloride solution or the administration of sodium chloride by mouth. In our experience, these animals often secrete small volumes of gastric juice, ranging between 75 and 300 cc. each day. It may be that in the presence of this small loss of gastric juice the sodium chloride in the food is sufficient for replacement.

THE EFFECT OF ALTERATION IN THE CHEMICAL STRUCTURE OF THE BLOOD ON GASTRIC SECRETION

In many of the reported studies on the physiology of gastric secretion in man and in experimental animals, little attention has been paid to the chemical structure of the blood at the time the experiments have been performed. When small Pavlov pouches are made, or only small samples of gastric secretion are removed from the body, this factor is probably of little importance. When, however, studies are made on animals with a totally isolated stomach or with a large Pavlov pouch, the chemical

structure of the blood and the state of hydration of the animal are the most important factors determining the volume of gastric juice produced in a twenty-four hour period. Thus, if care is taken to administer intravenously a quantity of isotonic sodium chloride solution equivalent to, or somewhat in excess of, the amount of gastric juice produced during the twenty-four hour period, gastric secretion is maintained at a relatively constant level from day to day. This is true in spite of great variation in the amount of food ingested. If the parenteral administration of sodium chloride solution or the addition of sodium chloride to the food is omitted, the volume of gastric secretion promptly decreases, until after five or six days only one half to one third of the previous amount may be collected. The minimum average secretions listed in

TABLE 4.—*Effect of Electrolyte Depletion on Gastric Secretion in a Dog with a Vagally Innervated Total Pouch**

Period of Collection, Hr.	Weight Kg.	Food		Water by Mouth, Cc.	Ringer's Solution Intravenously, Cc.	Sodium Chloride by Mouth, Gm.	Gastric Juice, Cc.
		Milk, Cc.	Meat, Gm.				
			Dog. No. 7				
24	11.4	400	445	3,000	1,000	4	1,604
24	11.2	400	500	2,160	1,000	4	1,146
24	11.0	400	102	1,500	1,000	4	1,080
24	10.8	106	397	1,632	1,000	4	1,460
24	11.2	200	530	2,810	1,000	5	982
24	11.5	0	500	1,412	0	0	1,182
24	11.5	0	418	1,500	0	0	1,000
24	11.0	0	492	1,500	0	0	648
24	10.9	0	304	542	0	0	410
24	10.8	0	130	607	0	0	295

* The animal became depressed, refused all food and died three days later.

tables 1, 2 and 3 were obtained under these conditions. It is true, however, that when the replacement of sodium chloride in these animals is discontinued, a loss of appetite and decreased ingestion of food often occur and are perhaps partially responsible for the decreased secretion.

The following protocols and table 4 illustrate the effects of chloride depletion on gastric secretion in dogs with total isolated stomach pouches or large Pavlov pouches:

Dog 1.—Isolated stomach with vagi intact. This animal secreted an average of 800 cc. of gastric juice each day for a ten day period while receiving daily intravenous injections of 2,000 cc. of Ringer's solution in addition to food. During this period, the blood chloride content was 79 milliequivalents and the p_H 7.63. The use of Ringer's solution was discontinued, and the gastric secretion gradually decreased to 260 cc. per day. The blood chloride content fell to 52 milliequivalents, and the p_H rose to 7.73.

Dog 2.—Isolated stomach with vagi intact. This dog secreted an average of 980 cc. of gastric juice each day while receiving 2,000 cc. of Ringer's solution

daily. The blood chloride level was 77 milliequivalents and the p_H 7.45. Administration of Ringer's solution was discontinued for five days; the secretion fell to 275 cc. per day and the blood chlorides to 50 milliequivalents, and the p_H rose to 7.67.

Dog 3.—Large Pavlov pouch. This dog secreted the surprising total of 1,900 cc. of gastric juice daily while receiving 2,000 cc. of Ringer's solution by vein. The blood chloride level was 91 milliequivalents and the p_H 7.40. Administration of Ringer's solution was discontinued for two days; the gastric secretion decreased to 565 cc. per day, and the blood chlorides to 39 milliequivalents, and the p_H rose to 7.54.

TABLE 5.—*Effect of Fasting on Gastric Secretion in Dogs with Vagally Innervated Total Pouches*

Period of Collections, Hr.	Food		Ringer's Solution Intravenously, Cc.	Sodium Chloride by Mouth, Gm.	Water by Mouth, Cc.	Gastric Juice, Cc.
	Meat, Gm.	Milk, Cc.				
			Dog. No. 4			
24	150	600	2,000	..	1,200	1,006
24	226	400	1,000	..	800	920
24	130	600	2,000	..	1,000	640
24	None	None	2,000	..	800	565
24	None	None	2,000	..	1,200	710
24	356	300	2,000	..	1,200	880
24	550	100	1,000	..	1,400	530
24	520	200	2,000	..	1,200	610
			Dog. No. 5			
24	600	275	.....	5	1,600	620
24	520	200	.....	5	800	560
24	500	300	.....	5	1,000	420
24	None	None	2,000	..	1,600	416
24	None	None	2,000	..	1,600	485
24	786	200	.....	5	1,600	456
24	594	250	.....	5	1,600	510
24	520	200	.....	5	1,400	500

THE EFFECT OF FASTING ON GASTRIC SECRETION IN TOTAL POUCH DOGS

One of the striking findings in the gastric secretion of dogs with the vagally innervated isolated stomach is the relatively slight effect of fasting on the output of gastric juice when the blood electrolytes are maintained. This is illustrated in tables 5 and 6. Dog 4 secreted 565 and 710 cc. and dog 5 secreted 416 and 485 cc. of gastric juice on days when no food was given. These amounts are only slightly less than those obtained when the animals were fed. During the fasting period, the blood chloride of dog 4 was 95 milliequivalents and the carbon dioxide capacity 70.4 cc.; the blood chloride of dog 5 was 108 milliequivalents and the carbon dioxide capacity 55.8 cc. per hundred cubic centimeters. Thus even 2,000 cc. of Ringer's solution given intravenously each day was not adequate to maintain a normal level of blood chloride. In dog 6 (table 6) the gastric secretory output was 1,190 and

1,206 cc. on the two days before the fast, and on the day when no food was given 905 cc. was secreted. It is important to point out that during this fasting period neither Ringer's solution intravenously nor sodium chloride by mouth was given as replacement therapy.

OCCURRENCE OF PEPTIC ULCERS IN THE VAGALLY INNERVATED ISOLATED STOMACH

In 1935 Dragstedt [15] reported the development of typical progressive peptic ulcers in 7 animals provided with vagally innervated isolated stomachs. In each instance the ulcer appeared in the isolated stomach, which, of course, took no part in the digestion of food. These findings

TABLE 6.—*Effect of Fasting on Gastric Secretion in Dogs with Vagally Innervated Total Pouches*

Period of Collection, Hr.	Food		Ringer's Solution Intravenously, Cc.	Sodium Chloride by Mouth	Water by Mouth	Gastric Secretion		
	Meat, Gm.	Milk, Cc.				Volume, Cc.	Free Hydrochloric Acid, %	Total Chlorides, Mg. per 100 Cc.
				Dog No. 6				
24	522	250	2,000	0	1,600	1,450	.....	...
24	604	250	2,000	0	1,800	760	.....	...
24	610	250	2,000	0	1,820	1,190	.....	...
24	614	250	2,000	0	1,800	1,206	.....	...
24	0	0	0	0	800	905	0.312	548
24	352	250	0	0	1,150	770	0.336	532
24	0	0	0	0	930	690	0.201	535
24	622	200	1,000	0	1,800	695	0.332	554
24	620	250	2,000	0	1,800	1,290	0.383	554
24	576	250	2,000	0	2,000	1,415	0.398	567
24	606	250	2,000	0	1,850	850	0.361	567
24	667	250	2,000	0	2,000	1,295	0.398	559

have been repeatedly confirmed. As a matter of fact, the chief difficulty that we experience in the use of the preparation in the study of gastric secretion arises from this complication. Sooner or later such ulcers develop in the great majority of these animals and they die as a result of hemorrhage or perforation. In general, the ulcers appear more rapidly in animals which secrete large volumes of gastric juice. This has become evident with our increasing use of the preparation illustrated in figure 5, where the antrum is anastomosed to the esophagus. In several cases large bleeding ulcers have appeared in the isolated stomach within two weeks after the operation. Usually, however, an interval of four to eight weeks intervenes between the preparation of the isolated stomach and the appearance of the ulcer. During this time the gastric juice is water clear, with suspended flakes of fibrin. Blood in the gastric juice heralds the ulcer and this progresses rapidly, with marked deterioration of the

15. Dragstedt, L. R.: Ann. Surg. **102**:563, 1935.

animal brought about by anemia and anorexia. The lesion commonly appears in the main body of the isolated stomach (fig. 6) and only rarely in the suture line.

While the incidence of ulcers is particularly high in the vagally innervated isolated stomach, they do occur in the Pavlov pouch and may attain large size (fig. 7). At least 6 such ulcers have been noted in this laboratory. They are especially apt to develop where a large pouch has been made and an abundant secretion of gastric juice obtained. In such cases a broad isthmus has been provided, with preservation of more than the usually meager vagal innervation. This point becomes of unusual significance when viewed in the light of reports from the

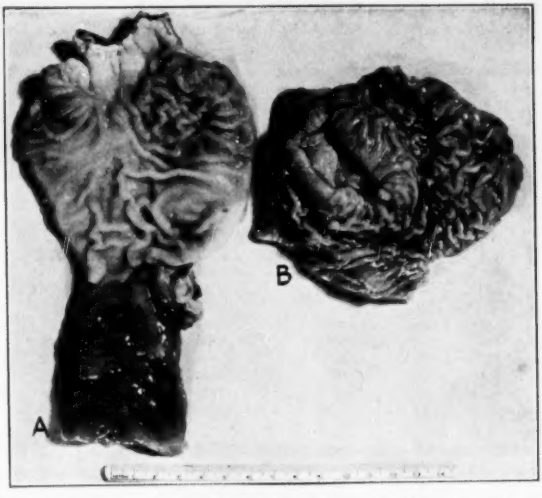

Fig. 6.—A large ulcer in the fundus of the stomach (*B*) that has been isolated as in figure 5; *A* illustrates the esophagus above anastomosed to the antrum with the duodenum below.

clinic of favorable results from gastric vagotomy in the treatment of peptic ulcer. In our experience, preservation of vagal innervation has been essential for the development of ulcers in either the isolated whole stomach or the Pavlov pouch. Similar preparations with the vagus nerves sectioned or crushed have never yielded these lesions. The most obvious explanation for this difference depends on the greater secretory activity of the preparation with the vagi intact. Other factors not immediately apparent may be involved, however, and these may prove susceptible of study by these methods.

If a large cannula is placed in the isolated stomach or Pavlov pouch, the interior can be readily examined with a cystoscope. We have done

this a number of times. Occasionally an ulcer may be detected when small, scarcely more than an erosion, and then observed as it rapidly progresses to a large size with profuse hemorrhage and subsequent perforation.

COMMENT

The totally isolated stomach, with preservation of its blood and nerve supply, is for some purposes the most satisfactory preparation for the study of gastric secretion. By the method described, a quantitative collection of all gastric juice secreted for periods of many weeks or months is readily accomplished. A comparison of the day and night secretion may be easily made. The volume of gastric juice secreted by

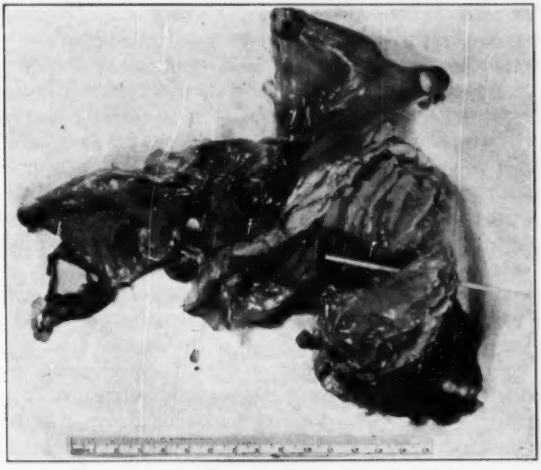

Fig. 7.—A large ulcer with perforation (illustrated by probe) occurring in a Pavlov pouch.

such a preparation is surprisingly large and confirms the results previously reported by Dragstedt and Ellis.[8] When the entire stomach was excluded and the esophagus united to the duodenum or jejunum, a maximum of 1,790 cc. of gastric juice in twenty-four hours was secreted by 1 animal, with an over-all average of 906 and 973 cc. for all the dogs. When, however, the antrum was united to the esophagus and the remainder of the stomach isolated, a maximum of 3,245 cc. in twenty-four hours was obtained from 1 animal. The average of the maximum twenty-four hour secretions of the animals with this preparation was 1,687 cc., or about 75 per cent more than was secured when the antrum was isolated and prevented from coming into contact with food. This finding strongly supports the concept of Edkins that the antrum plays

a special role in gastric secretion and indicates furthermore that it is more important than the mucosa of the entire intestinal tract. It does not, however, provide any data concerning the mechanism of action of the antrum, i. e., whether this is by means of a hormone, nervous reflexes or mechanical distention.

The criticism may be offered that these large volumes of gastric secretion occur when extensive injections of Ringer's solution are made or generous amounts of sodium chloride are provided by mouth. This is true. When salt replacement is discontinued, the secretion of gastric juice promptly falls off, and when hypochloremia, alkalosis and dehydration develop, the output of gastric juice may be decreased 75 per cent or more. However, under normal conditions the gastric juice flows into the intestines and is reabsorbed; hence automatic salt replacement is the normal process. It may well be that the small volumes of gastric juice often encountered in dogs with isolated stomachs or Pavlov pouches when salt replacement is not adequate are actually abnormal and depend in large part on chloride depletion. It must be conceded that in many cases we have administered more electrolyte in the form of Ringer's solution or sodium chloride by mouth than has been excreted by the isolated stomach. However, in spite of this large supply, the blood chloride has usually remained below the normal level. The question as to whether or no the administration of excess salt will stimulate gastric secretion is being presently studied in our laboratory.

The possibility that the large volumes of gastric secretion reported in this paper as well as those previously recorded by Dragstedt and Ellis [8] are due to constant stimulation of the vagi by traction or scar tissue is very improbable. Similar or almost as large volumes may be obtained from large Pavlov pouches when salt replacement is carefully conducted. It is more likely that even the large volumes of gastric juice secreted by these vagally innervated isolated stomachs are actually less than the amounts normally produced by the intact stomach. In the former case the salt replacement is intermittent rather than continuous and the possible stimulating effect of the presence of food in the main body of the stomach is absent. It should be emphasized that when sufficient electrolyte is supplied, the dog with a totally isolated stomach usually remains in a good nutritive state and may gain in weight. It is by no means the unphysiologic preparation that some have supposed and should be more widely used in studies on gastric secretion and mineral metabolism.

The conclusion of Dragstedt and Ellis [8] that progressive hypochloremia, alkalosis and dehydration will develop in these animals and that they will die if adequate salt replacement is not carried out has been repeatedly confirmed. These data plus the well established similar chemical alterations in the blood following pyloric obstruction or gastric fistula, in both man and experimental animals, leave little doubt con-

cerning the fatal effect of the total loss of gastric juice and the necessity for its absorption in the intestines. Apparently, however, in some circumstances the secretion of gastric juice may be so greatly suppressed that its total loss may be tolerated for relatively long periods. This is possibly the explanation for the reported long survival of animals with high intestinal obstruction when salt solution is given parenterally during the early postoperative period. It may also account for the survival of dogs in which esophagotomy, pyloric obstruction and gastric and intestinal fistula have been carried out in the experimental work of Webster and Armour.[9] It is certainly true in many cases in which, after vagal denervation, dogs with totally isolated stomachs survive indefinitely and yet lose all the gastric juice they secrete. In these cases the sodium chloride in the diet suffices to replace the loss of chloride in the small volumes of gastric juice produced.

The marked decrease in gastric secretion which occurs when hypochloremia and alkalosis develop has, of course, a protective effect. It suggests that the parietal cells find difficulty in manufacturing hydrochloric acid when the concentration of chloride in the plasma is reduced and the blood is more alkaline. Pavlov's contention that the gastric glands secrete gastric juice with a constant concentration of hydrochloric acid is true when the chemical structure of the blood is normal, but when pronounced hypochloremia exists the concentration of acid in the fundus secretion is likewise reduced but to a lesser degree.

The persistence of a relatively large volume of gastric secretion in dogs with vagally innervated total pouches during fasting is striking and merits further investigation. In many instances these animals secrete almost as much gastric juice in a twenty-four hour period when no food is given as they do when they consume the regular diet. Psychic stimuli are undoubtedly a factor, since these animals can see and smell the food given to the dogs in neighboring cages. The contrast with Pavlov pouch dogs in this respect, however, is marked, since in the same environment fasting produces a notable decrease in secretion in these animals. This may be due to the poor vagal innervation of the Pavlov pouch as compared with the totally isolated stomach.

The great frequency with which progressive peptic ulcers appear in vagally innervated isolated stomachs is a drawback to the use of this preparation in the study of gastric secretion but of great interest in the problem of the cause of ulcer itself. It confirms the view previously expressed [16] that pure gastric juice has the capacity to digest all living tissue, including the wall of the stomach itself. This fact must be taken into consideration in theories advanced to account for the secretion of hydrochloric acid and pepsin by the gastric glands.

16. Dragstedt, L. R.: Pathogenesis of Gastroduodenal Ulcer, Arch. Surg. **44**:438 (March) 1942.

CONCLUSIONS

1. Total isolation of the stomach in dogs, with preservation of blood and vagus nerve supply, permits the quantitative collection of the gastric secretion for periods of weeks or months.

2. Such isolated stomachs may secrete a maximum average of 906 and 973 cc. of gastric juice in twenty-four hours when the alimentary tract is reconstructed by anastomosis of the esophagus with the side of the jejunum or the end of the duodenum.

3. When the fundus alone is isolated and the esophagus is united with the gastric antrum, a maximum average of 1,687 cc. of gastric juice in twenty-four hours may be obtained, which indicates the stimulating effect of the antrum on gastric secretion when it comes into contact with the ingested food.

4. The continued secretion and loss of these large amounts of gastric juice produce progressive hypochloremia, alkalosis, dehydration, azotemia and death in from four to twelve days when the only salt supplied is that present in the stock diet.

5. These chemical changes in the blood can be prevented and life preserved for long periods by the intravenous injection of 1,000 to 2,000 cc. of isotonic sodium chloride solution or the addition of 10 to 15 Gm. of sodium chloride to the diet each day.

6. Cessation of salt replacement even after five or six months results in prompt demineralization, dehydration and death.

7. The development of hypochloremia, alkalosis and dehydration produces prompt and marked reduction in the volume of gastric juice secreted in a twenty-four hour period and also reduction in the concentration of hydrochloric acid in the parietal secretion.

8. Under these conditions of depressed secretion, the intravenous injection of salt solution or administration of sodium chloride by mouth causes a considerable increase in the volume and acidity of the gastric juice.

9. When adequate salt replacement is carried out and dehydration is prevented, the volume and acidity of the gastric secretion are but slightly reduced by fasting for twenty-four or forty-eight hours. This is in decided contrast to the great reduction in gastric secretion produced by fasting in Pavlov pouch dogs or in animals with vagally denervated total pouches.

10. Progressive typical peptic ulcers regularly appear in the vagally innervated isolated stomach in from one week to several months and cause death from hemorrhage or perforation. Such ulcers also occur in large, actively secreting Pavlov pouches but have not been seen in similar preparations in which the vagus nerves have been divided. The occurrence and progression of the ulcers can be observed by means of a cystoscope introduced through the cannula into the isolated stomach.

SURGERY OF THE BILIARY TRACT

A Five Year Survey

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THIS report is a study of 533 patients who underwent 550 operations on the biliary tract during the five year period beginning January 1940 and ending December 1944 at the Cedars of Lebanon Hospital. The series includes multiple operations on 17 patients. All operative procedures on the biliary tract are included. These operations were carried out by the various members of the attending and house staffs on both private and clinic patients.

Of the 533 patients, 406 (76 per cent) were women and 127 (24 per cent) were men (table 1). The ratio of women to men was approximately 3:1.

The incidence of jaundice is interesting. Of the 533 patients, 110 (20.7 per cent) were jaundiced preoperatively. Of these 110, 66 (60 per cent) were women and 44 (40 per cent) were men. The ratio of jaundiced women to jaundiced men is 3 to 2. It is interesting to note that although approximately three times as many women were operated on as men, the relative incidence of jaundice is higher among men. This is in accordance with the findings of the Mayo Clinic.[1]

OPERATIONS FOR BENIGN LESIONS OF THE BILIARY TRACT

Cholecystectomy was done 387 times, with 8 hospital deaths, a mortality rate of 2.1 per cent. This was accomplished with the lowest mortality rate of all operative procedures (table 2). Cholecystostomy was done on 29 patients, with 2 deaths, a mortality rate of 7.0 per cent. Brooks and Wyatt[2] reported the performance of cholecystostomy on 54 patients, with a mortality rate of 14.5 per cent. Heyd, Carter and

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From the Surgical Services of the Cedars of Lebanon Hospital.

1. (*a*) Walters, W.; Gray, H. K., and Priestley, J. T.: Lesions of the Biliary Tract for 1940, Proc. Staff. Meet., Mayo Clin. **16**:681-687, 1941. (*b*) Walters, W.; Gray, H. K.; Priestley, J. T., and Counsellor, V. S.: Lesions of the Biliary Tract for 1941, ibid. **17**:545-550, 1942.

2. Brooks, B., and Wyatt, T. E.: Surgery of the Gall Bladder, Ann. Surg. **109**:334-350, 1939.

Hotz [3] reported 88 cholecystostomies, with 26 deaths, a mortality rate of 29.5 per cent.

In our series the second lowest mortality rate occurred when cholecystectomy and choledochostomy were performed. These procedures were carried out on 87 patients, with 3 deaths, a mortality of 3.4 per cent. Heyd and his co-workers [3] reported on 238 patients who underwent this operative procedure for chronic disease of the gallbladder, with 27 deaths, a mortality rate of 11.3 per cent and 89 patients on whom the same operations were performed for acute cholecystitis, with 13 deaths,

TABLE 1.—*Distribution According to Sex and Incidence of Jaundice*

	Number of Patients	Percentage of Total	Ratio
Female	406	76	3
Male	127	24	1
Total	533		
Jaundiced patients			
Female	66 (60%)	..	3
Male	44 (40%)	..	2
Total	110	20.7	

TABLE 2.—*Hospital Mortality in Relation to Operative Procedures for Benign Lesions*

	Total Number of Operations	Hospital Deaths	Mortality Rate, Percentage
Cholecystectomy	387	8	2.1
Cholecystostomy	29	2	7.0
Choledochostomy	16	1	6.3
Cholecystectomy and choledochostomy	87	3	3.4
Cholecystostomy and choledochostomy	6	1	16.7
Stricture of common duct	5	1	20.0
Transduodenal choledochostomy	3	1	33.3
Total	533	17	3.2

or a mortality rate of 14.6 per cent. Brooks and Wyatt [2] reported 15 cases, with 3 deaths, a mortality rate of 20 per cent.

Cholecystostomy and choledochostomy were performed on 6 patients in our series, with 1 death, a mortality rate of 16.7 per cent. This is similar to the mortality rates reported by other authors.[4]

3. Heyd, C. G.; Carter, R. F., and Hotz, R.: Surgery of the Biliary Tract: A Study of the Factors in Surgical Morbidity and Mortality, Am. J. Surg. **44**: 677-719, 1939.

4. (*a*) Maes, U., and Romano, S. A.: Biliary Tract Surgery, Rev. Gastroenterol **8**:245-255, 1941. (*b*) Brooks and Wyatt.[2] (*c*) Heyd and others.[3] Heyd, C. G.: Factors in Mortality in 4,000 Operations on the External Biliary System, Ann. Surg. **111**:820-830, 1940.

Transduodenal choledochostomy was done in only 3 cases, with 1 death, giving a 33 per cent mortality rate. This is too small a series of cases to be statistically significant. The mortality rates for the various other procedures carried out are shown in table 2.

Among the 533 patients with benign lesions of the biliary tract there were a total of 17 hospital deaths, or a mortality of 3.2 per cent. This compares favorably with a similar series at the Mayo Clinic [1a] and a series of Maes and Romano [4a] at the Charity Hospital in New Orleans, who found a mortality rate of 7.0 per cent. It also compares favorably with the figures given by other authors.[5]

JAUNDICE AND PATHOLOGIC CHANGES IN THE COMMON DUCT

With surgery of the biliary tract now in its third era,[6] there is an increasing tendency to explore the common duct. Eliason and North [7] gave the following indications for exploration: (1) a history of jaundice and of acholic stools; (2) stones palpable in the common duct, and (3) a common duct which is dilated, thickened and white or gray in color instead of its normal bluish color. Eliason and Erb [8] report explorations of the common duct in 18 per cent of their series of cases, and stones were found in 60 per cent of the cases. Walters [9] stressed the importance of palpable stones and changes in the color or size of the duct as indications for exploration. Walters and Gray [10] reported a series in which 182 patients, or 22 per cent, had undergone exploration of the common duct and stones were found in 60 per cent. Lahey [6] has long advocated more frequent exploration of the common duct. He advised immediate inspection of the contents of the gallbladder and felt that marked evidence of long-standing infection in the gallbladder wall, such as thickening and fibrosis or the presence of thick, black, tenacious bile, may be an indication for exploration. He suggested aspiration of the duct with a needle and syringe when doubt exists; if the bile is cloudy or black or contains flocculi, stones will usually be present. When such infected bile is present, even though stones are not found, opening and

5. Bachhuber, C. A.: Surgery of the Biliary Tract, M. Times **68**:3-6, 1940.

6. Lahey, F. H.: The Third Era in the Surgical Treatment of Cholelithiasis: Removal of All Stones in the Ducts, Surg., Gynec. & Obst. **67**:698-700, 1938.

7. Eliason, E. L., and North, J. P.: Early Surgery in Biliary Disease, Surg., Gynec. & Obst. **68**:167-178, 1939.

8. Eliason, E. L., and Erb, W.: Mortality in Surgery of Biliary Tract, Ann. Surg. **101**:460-468, 1935.

9. Walters, W.: Personal Experiences in the Treatment of Benign Obstructing Lesions of the Biliary Tract, Surgery **3**:884-892, 1938.

10. Walters, W., and Gray, H. K.: Annual Report for 1936 of Surgery of Stomach, Duodenum and Biliary Tract, Proc. Staff. Meet., Mayo Clin. **12**:561-565, 1937.

draining the duct will still help the patient. He estimated that he explores the common duct in about 50 per cent of the operations on the biliary tract and that stones are found in about one half of the cases. A recent report [11] from the Lahey Clinic gives the same figures.

During the five year period of this survey there were 101 (19 per cent) cases in which exploration of the common duct was carried out (table 3). One hundred and ten patients were jaundiced preoperatively. The common duct was explored 67 times (61 per cent of the jaundiced patients), and a stone was found in about half the patients. In 43 jaundiced patients the common duct was not explored, as outlined in table 5, because the surgeon apparently felt that it was not indicated on

TABLE 3.—*Relation of Jaundice to Stones in the Common Duct.*

Jaundice	Common Duct		Stones in the Common Duct		Incidence of Stones, Percentage
	Not Explored	Explored	Present	Absent	
Present					
110 cases	43 (see table 5)	67	33	34	49
Absent					
423 cases	389	34	8	26	23
533 Total	..	Total 101 (19% of 533)	41	60	..

TABLE 4.—*Levels of Icteric Index*

	Common Duct Not Explored	Common Duct Explored	
		Stones Absent	Stones Present
Average	24	35	41
Highest	47	80 (Pancreatitis)	110

the basis of the patient's history or because at operation the duct appeared normal in size and color. In some cases the jaundice was due to a perforated gallbladder with localized inflammation or abscess. It was surprising to follow the hospital course of these 43 jaundiced patients (39 per cent of the total number of jaundiced patients) and find that the jaundice disappeared without surgical intervention on the common duct. A comparison was then made of the degrees of jaundice (table 4). It was found that an average icteric index in this group of cases was 24, whereas in the group in which the common duct was explored the average was 38 (35 when stones were absent and 41 when stones were present).

11. Adams, R., and Stranahan, A.: Cholecystitis and Cholelithiasis, **Surg.**, Gynec. & Obst. **85**:776-784, 1947.

It is interesting to note that in the group of cases in which exploration of the common duct was not done the icteric index rose as high as 40 in 1 case, the highest being 47, and then fell during the postoperative period. A follow-up study will be done in the near future to determine whether this group required additional surgical procedures subsequently. In the groups in which the common duct was explored the highest icteric index in the absence of stones in the common duct was 80 (due to pancreatitis), whereas the highest in the presence of stones was 110. The highest index of jaundice of all the cases studied was 238; it occurred in a case of benign stricture of the common duct. The next highest were 130 and 132, which occurred in cases of carcinoma of the gallbladder and the head of the pancreas.

These findings are in accordance with what Glenn [12] and others have pointed out, namely, that the "duct may be indurated and may appear

TABLE 5.—*Operative Findings in Jaundiced Patients Not Subjected to Exploration of the Common Duct*

1. Cholecystectomy without indication for exploration of the common duct			15*
2. Benign stricture of common duct			8*
3. Malignant process:	(a) Carcinoma of head of pancreas	7	
	(b) Carcinoma of gallbladder	2	
	(c) Carcinoma of ampulla of Vater	1	
	(d) Lymphosarcoma	1	
	Total	11	11
4. Perforation of gallbladder			4
5. Cirrhosis of liver			3
6. Pancreatitis			2
7. Infectious hepatitis			1
8. Patient's condition too poor for exploration of common duct			1
Total			45

* One patient also had cirrhosis.

to be distended without harboring a stone. An icteric index of 30 or less may be due to an inflammatory process in the biliary tree rather than to obstruction of the duct by stone." Glenn stated that the common duct should not be explored in the presence of acute cholecystitis unless exploration is definitely indicated. This should be kept in mind in all acute or subacute inflammatory conditions of the biliary tract and will help to decrease the number of explorations of the common duct done for stones when none is present.

A study of table 3 reveals that in the 110 cases of jaundice stones in the common duct accounted for the condition in only 33 (30 per cent). In other words, the jaundice in 70 per cent of the 110 cases apparently was due to inflammation or edema of the ducts or to hepatic damage. These findings indicate that the presence or absence of jaundice is an important but a treacherous signal.

12. Glenn, F.: Acute Cholecystitis, Surg., Gynec. & Obst. **69**:431-435, 1939.

In addition to the 67 cases in which exploration of the common duct was performed in the presence of jaundice, there were 34 cases in which exploration was done in the absence of jaundice, making a total of 101, which is 19 per cent of the total cases. Of the 34 cases, in only 8, or less than one fourth, was a stone found in the common duct. Thus there is twice as great a chance of finding a stone in the common duct in the presence of jaundice as there is in the absence of jaundice.

A study of the distribution of ductal explorations by decades (table 6) shows that, except for the unusually high incidence (33.3 per cent) in the third decade, there is a gradually rising incidence with each decade: 13, 18 and 19 per cent, until it jumps to 30 and 33.3 per cent in the seventh and eighth decades.

In almost every case of exploration of the common duct a T tube or a catheter was inserted into the duct. In some cases immediate cholangiographic examination (as suggested by Mirizzi [13]) was done on the operating table in order to detect stones. In most cases delayed

TABLE 6.—*Exploration of Common Duct by Decades*

Ages	20-29	30-39	40-49	50-59	60-69	70-79
Number of cases	8	13	28	29	24	8
Percentage	33.3	13	18	19	30	33.3

cholangiographic examination was done two to three weeks postoperatively before the T tube was removed. The postoperative study is useful not only to detect stones but also to determine whether spasm of the sphincter of Oddi is present. When stones were left in the common duct a combination of Best's [14] regimen and ether and alcohol injections (Pribram [15] and Walters [16]) into the duct via the T tube was tried in an attempt to dissolve or dislodge them.

MORTALITY

There was a total of 17 hospital deaths among the patients with benign lesions of the biliary tract. Eight of the patients who died were jaundiced preoperatively, and 9 were not (table 7). It is seen that the hospital mortality rate in the presence of jaundice was 7 per cent, while the mortality rate in the absence of jaundice was 2.1 per cent.

13. Mirizzi, P. L.: Operative Cholangiography, Surg., Gynec. & Obst. **65**: 702-710, 1937.

14. Best, R. R., and Hicken, N. F.: Biliary Dyssynergia, Surg., Gynec. & Obst. **61**:721-734, 1935.

15. Pribram, B. O.: New Methods in Gall Stone Surgery, Surg., Gynec. & Obst. **60**:55-60, 1935.

16. Walters, W.: Recent Advances in Surgical Treatment of Lesions of the Biliary Tract, Surgery **3**:786-798, 1938.

Thus, the jaundiced group had a mortality rate more than three times as great as that of the nonjaundiced group.

Table 8 is a detailed study of the causes of death in patients with benign lesions. These deaths are further subdivided into those which could be attributed to local complications and those due to systemic complications. It can be seen that 9 patients died of systemic complications and 7 died of local complications. In 1 case the cause of death was unknown. There were 2 cases of cerebrovascular accidents and 1 of bronchopneumonia. In 1 patient evisceration occurred, and reoperation

TABLE 7.—*Benign Lesions: Hospital Deaths in Relation to Jaundice*

	Number of Deaths	
Jaundice present	8	7.0% of jaundiced group
Jaundice absent	9	2.1% of nonjaundiced group
Total	17	3.2% of all patients

TABLE 8.—*Summary of Hospital Deaths Among Patients with Benign Lesions*

Systemic Causes		Hospital Number	Deaths, Percentage
Cerebrovascular accident		2	11.8
Bronchopneumonia		1	5.9
Evisceration and intestinal obstruction		1	5.9
Mortality within first 24 hours		3	17.5
Mortality within first 48 hours		2	11.8
Local Causes			
Infections			
Subphrenic abscess	1		
Subphrenic abscess with duodenal fistula	1		
Subphrenic abscess with portal thrombosis	1		
Peritonitis	1		
Total	4	4	23.5
Duodenal fistula and pulmonary embolus		1	5.9
Hepatorenal syndrome		1	5.9
Hepatorenal syndrome with portal thrombosis		1	5.9
Unknown		1	5.9
Total		17	100.0

was required on the twenty-fourth postoperative day for intestinal obstruction. In this patient a right rectus incision had been made. He died eighteen days after the second operation. Autopsy showed recurrent partial obstruction and embolus of the superior mesenteric artery. Three patients died within twenty-four hours, and 2 more died within forty-eight hours. There were 4 deaths directly or indirectly attributable to infection: 1 to peritonitis and 3 to subphrenic abscesses, 1 with duodenal fistula and another with portal thrombosis. With the recent addition of streptomycin to the surgeon's armamentarium, the deaths from infections may be decreased. One fatality was due to pulmonary embolus. The explanation of this extremely low incidence of pulmonary embolus may be due to the general policy of early ambulation at the hospital,

associated with the observed lower incidence of thromboembolic disease in this warmer climate. Two patients died on the third postoperative day with a clinical diagnosis of hepatorenal syndrome.

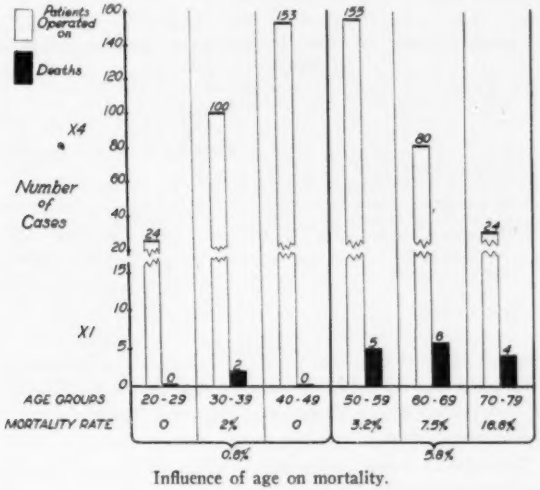
Of the 17 patients who died, 10 had involvement of the common duct as follows: (1) operations on the common duct were done, (2) secondary operation was necessary for a stone left in the common duct, (3) there was injury of the common duct or (4) stone was found in the common duct at autopsy.

Heyd has shown that disease of the gallbladder is a continuing and progressive condition. This study bears out the progressive character of disease of the biliary tract. An example is case 65606. This is the case of a 29 year old woman who had a cholecystographic examination in 1923 for heartburn and epigastric distress. The roentgenograms were normal. In 1929, six years later, she complained of epigastric pain radiating to the back. Repeat roentgenograms showed a "sluggish" gallbladder and pylorospasm. In 1933, four years later, she was given roentgenologic examination again for the continuation of her symptoms. It showed a poorly functioning gallbladder without stones. Her symptoms gradually grew worse, until finally recurrent attacks of pain developed in the right upper quadrant. In 1939, sixteen years after the first roentgenograms of the gallbladder, another series showed a diseased gallbladder with one large stone. Cholecystectomy was done. This case demonstrates the progression from biliary dysfunction to cholecystitis, formation of stones and severe cholecystitis with acute attacks. The next stages in progression of the disease would be involvement of the common duct, i. e., dilatation, bile stasis, formation of stones, infection and periods of obstruction which might go on to damage of the liver and pancreas.

The accompanying chart shows the distribution of the patients with benign lesions according to age groups. A study of this chart reveals an increase in the number of patients operated on from the third to the fifth decade of life; in the sixth decade the level is maintained, and then there is a corresponding fall in the seventh and eighth decades, so that there were 277 operations on patients below the age of 50 and 259 operations on patients over the age of 50.

There were 2 fatalities in 277 patients below the age of 50 (0.6 per cent mortality rate). One patient had an icteric index of 80. Cholecystectomy and choledochostomy were done. A stone was removed from the common duct, and a T tube was inserted. The patient died thirty days after operation. Autopsy showed a left subphrenic abscess, pulmonary abscess and bronchopneumonia. In the other patient accidental ligation of the common duct occurred in the course of cholecystectomy. On the thirty-third postoperative day the common duct was reconstructed. She died fifteen days after the second operation. Permission for autopsy was not obtained.

It has been said that the surgical risk is doubled at the age of 50, tripled at 60 and quadrupled at 70. The rising mortality rate, 3.2 per cent in the sixth decade, 7.5 per cent in the seventh decade and 16.6 per cent in the eighth decade, in our series bears out this general statement, but the rate is increased to an even greater degree. There were 15 fatalities in 259 patients over the age of 50. This is a mortality rate of 5.8 per cent, almost ten times as great as the mortality rate in patients below the age of 50. Of the 15 patients, 8 had been subjected to operation on the common duct. In table 6 it can be seen that there were 49 ductal exploration in patients below the age of 50, whereas in patients over that age there were 61.



Influence of age on mortality.

With the increase in the number of years that the disease has been present, several things occur. The patient gets into the older age group, the incidence of involvement of the common duct increases and progressive damage occurs to the gallbladder, liver and pancreas. Probably the best way to decrease the mortality rate would be to operate earlier in order to reduce the lethal factors of (1) operation on patients in the older age groups and (2) operation on patients with involvement of the common duct.

One unusually interesting case was that of a 47 year old woman who had a long history of severe paroxysmal nocturnal hemoglobinuria. During the previous five months pain had developed in the right upper

quadrant. Roentgen study revealed a nonfunctioning gallbladder without stones. At operation stones were found in a chronically inflamed gallbladder.

There were 2 cases of intestinal obstruction due to gallstones, 1 of which was diagnosed preoperatively.

MALIGNANT LESIONS OF THE BILIARY TRACT

Seventeen patients underwent operation for malignant lesions, with 6 hospital deaths, or a mortality rate of 35.3 per cent (table 9). This mortality rate, of course, is much higher than that of the benign group of lesions. The various palliative procedures are shown with their respective hospital mortality rates. Of the 17 patients, 11, or 65 per cent, were jaundiced at the time of operation.

TABLE 9.—*Hospital Mortality in Relation to Operative Procedure for Malignant Lesions*

	Total Number of Operations	Hospital Deaths	Mortality Rate, Percentage
Cholecystogastrostomy	3	2	66.6
Cholecystoduodenostomy	5	0	0.0
Cholecystojejunostomy	2	1	50.0
Choledochogastrostomy	2	0	0.0
Choledochoduodenostomy	2	0	0.0
Cholecystectomy	2	2	100.0
Gastroenterostomy	1	1	100.0
Total	17	6	35.3

SUMMARY

1. Five hundred and thirty-three patients underwent 550 operations on the biliary tract at the Cedars of Lebanon Hospital during the first half of the present decade.

2. The ratio of women to men was approximately 3:1. The relative incidence of jaundice is higher among men.

3. The mortality rates for the various operative procedures are reported.

4. The common duct was explored in 19 per cent of the cases, and stones were found in 40 per cent of these.

5. Jaundice was due to stones in 30 per cent of the cases. There is twice as great a chance of finding a stone in the common duct in the presence of jaundice as there is in its absence. The mortality rate in the jaundiced group of patients was more than three times as great as that in the nonjaundiced group.

6. The mortality rate among patients over the age of 50 was almost ten times as great as the rate among patients below that age.

ACUTE APPENDICITIS

Evaluation of Factors Contributing to the Decrease in Mortality in a Municipal Hospital Over A Twenty Year Period

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THE PRESENT decade has witnessed a spectacular drop in the mortality rate of acute appendicitis. This is nationwide and is reflected in the reports of small institutions [1] as well as those of large centers. There were 14,113 fatalities due to appendicitis in the United States in 1939, while in 1946 there were only 5,285.[2] Commenting on this progress, the Metropolitan Life Insurance Company [3] stated: "There is good reason to believe that within the next few years appendicitis will be reduced to a very minor cause of death in our country, and that medical science and public health administration will close another important chapter in their history." That many factors are responsible for this improvement is illustrated by the divergence of surgical opinion on the role each has played. These tend to fall into four general headings: first, public health education with its resulting earlier seeking of treatment by patients; second, improved operative management with emphasis on the elimination of drains and greater use of the McBurney incision; third, the improved methods and agents in the field of preoperative and postoperative supportive therapy, and, fourth, sulfonamide compounds and antibiotics.

In the report of a study of the mortality rate at the Cook County Hospital, Meyer, Requarth and Kozoll [4] emphasized chemotherapy, nonintervention in patients with abscess, decreased use of drains and the use of the McBurney incision as the factors responsible for improve-

From the Fourth Surgical Division, Bellevue Hospital.

1. McCreery, J. A., in discussion on Schullinger,[5] p. 470.

2. National Office of Vital Statistics: Personal communication to the authors.

3. Statistical Bulletin of the Metropolitan Life Insurance Company: Appendicitis Mortality Near Vanishing Point, January 1947, vol. 28, pp. 7-8.

4. Meyer, K. A.; Requarth, W. H., and Kozoll, D. D.: Progress in the Treatment of Acute Appendicitis, Am. J. Surg. **72**:830-840 (Dec.) 1946.

ment. Schullinger's [5] study of thirty years' experience at the Presbyterian Hospital in New York city attributes the improved mortality rate primarily to improved preoperative and postoperative treatment and the use of the antibacterial agents. In reporting an 0.92 per cent mortality rate in 1,405 cases covering the ten year period 1937 to 1946, McClure [6] stressed the multiplicity of general measures whose improvement has contributed to the decrease in mortality rate and attributes little to sulfonamide drugs and antibiotics. Hoerr's [7] report from the Peter Bent Brigham Hospital covering the period 1941 to 1945 emphasizes the importance of the sulfonamide drugs used intravenously in the decreased mortality rate. Green and Watkins,[8] after their comprehensive study of 19,399 patients operated on in Cleveland from 1930 to 1942, concluded that spinal anesthesia, the McBurney incision and the decreased use of drains are responsible for the decreased mortality rates.

When the sulfonamide compounds came into general use in the treatment of appendicitis, we made a survey of the cases in the Fourth Surgical Division of Bellevue Hospital for the preceding twelve years (1928 through 1939) to provide a background for evaluation of these agents. The results of this series of 677 cases of acute appendicitis and its complications have been reported.[9] These cases were divided into two groups, those from 1928 through 1933 and those from 1934 through 1939. This was a natural division, as it was during the latter period that the present anesthesia department of Bellevue Hospital was founded, fluid and electrolyte replacement put on a sounder basis and the blood bank begun. The period 1940 through 1947 is marked not only by the advent of the sulfonamide compounds but also by the antibiotics, improved methods of intestinal intubation, better understanding of intestinal obstruction, early ambulation and improved intravenous administration of solutions for parenteral alimentation. During the entire twenty years covered by the three periods the same policy of early operation after correction of fluid and electrolyte balance has been pursued. For correlation, most of the factors studied in our earlier report have been reexamined during the 1940-1947 period.

5. Schullinger, R. N.: Observations on Mortality from Acute Appendicitis at a University Hospital 1916 to 1946, Ann. Surg. **126**:448-471 (Oct.) 1947.

6. McClure, R. D.: in discussion on Schullinger,[5] p. 468.

7. Hoerr, S. O.: Factors in the Reduction of Mortality in Acute Appendicitis. Surgery **22**:402-407 (Aug.) 1947.

8. Green, H. W., and Watkins, R. N.: Appendicitis in Cleveland, Surg., Gynec. & Obst. **83**:613-624 (Nov.) 1946.

9. Slattery, L. R., and Hinton, J. W.: Mortality Rate from Acute Appendicitis in a Municipal Hospital, Am. J. Surg. **57**:294-303 (Aug.) 1942.

MORTALITY RATES

During the twenty years 1928 to 1947 inclusive, 942 patients with acute appendicitis and its complications have been operated on in the Fourth Surgical Division of Bellevue Hospital, with a mortality rate of 4.1 per cent. The classifications acute appendicitis, localized peritonitis, abscess and spreading or generalized peritonitis have been followed throughout for uniformity. Localized and spreading peritonitis have likewise been considered as one because of the difficulty in accurate appraisal of the extent of peritonitis by the operators. No cases of chronic appendicitis or mechanical disorders have been included. Table 1 presents the mortality rate of each group over twenty years.

TABLE 1.—*Mortality of Appendicitis for 1928 to 1947 Inclusive.*

Diagnosis	Number of Cases	Number of Deaths	Mortality Rate
Acute appendicitis	684	9	1.3
Local peritonitis	102	4	3.9
Abscess	100	8	8.0
General peritonitis	56	18	32.1
All forms of peritonitis	158	22	13.9
Totals	942	39	4.1

TABLE 2.—*Mortality Rate by Periods.*

	1928 to 1933			1934 to 1939			1940 to 1947		
Diagnosis	No. of Cases	No. of Deaths	Deaths, %	No. of Cases	No. of Deaths	Deaths, %	No. of Cases	No. of Deaths	Deaths, %
Acute appendicitis	266	7	2.6	208	1	0.47	210	1	0.47
Local peritonitis	33	2	6.06	34	2	5.8	35	0	0.0
Abscess	69	6	8.6	19	1	5.2	12	1	8.3
General peritonitis	23	10	43.4	25	6	25.0	8	2	25.0
All forms of peritonitis	56	12	21.4	59	8	13.5	43	2	4.6
Totals	391	25	6.3	286	10	3.4	265	4	1.5

A breakdown of this material into the three periods previously mentioned shows a progressive decline in mortality rate. During the third period, 1940 through 1947, there were 265 patients operated on, the decreased incidence of appendicitis on our service necessitating an eight year interval to collect a sufficient number of cases for comparison with the earlier series. This decrease in admissions for appendicitis has occurred despite an increase in the yearly admissions to the Bellevue Hospital from 52,411 in 1928 to 60,574 in 1947, the peak years being 1940 and 1941, when there were 69,276 and 70,604 admissions respectively. This paradoxic situation is accounted for by World War II, with its departure of young adults into military service, and the tendency of families to move to more suburban areas as a result of slum clearance and improved economic conditions. The mortality rate is compared for each period in table 2, which shows an approxi-

mate halving of the total mortality rate in each successive period, the total mortality rate dropping from 6.3 per cent in the 1928-1933 period to 1.5 per cent in the 1940-1947 period. Comparison of the last two periods shows no striking change except in the decreased mortality rate for all cases of peritonitis, obviously due to the great decline in the number of patients with generalized peritonitis. The small number of patients with abscess and generalized peritonitis makes comparisons with preceding periods unsatisfactory.

The reason for the decreased total mortality rates is clarified by table 3. This shows a progressive increase in the proportion of patients with unperforated acute appendicitis and those with local peritonitis, the types associated with the lower mortality rates. There is a corresponding decrease in the proportion of patients with abscess and general peritonitis, the types accompanied with the higher mortality rates. This change in distribution of cases is at variance with the observation of Hoerr,[7] who found the same proportion of complicated

TABLE 3.—*Proportion of Cases in Each Classification for Each Period.*

	Acute Appendicitis		Local Peritonitis		Abscess		General Peritonitis	
Years	Cases	Percentage of Total	Cases	Percentage of Total	Cases	Percentage of Total	Cases	Percentage of Total
1928 to 1933	266	68.0	33	8.4	69	17.6	23	5.8
1934 to 1939	208	72.7	34	11.8	19	6.6	25	8.7
1940 to 1947	210	79.2	35	13.2	12	4.5	8	3.0

cases in an analysis of two five year periods, 1936 through 1940 and 1941 through 1945, at the Peter Bent Brigham Hospital, and of Meyer,[4] who found a decrease in the proportion of patients with acute nonperforative appendicitis compared to those with perforation and abscess in a survey of the years 1937 and 1938 and 1944 and 1945 at the Cook County Hospital.

MORTALITY RATE AND EXPERIENCE OF OPERATOR

In the first twelve years of this study the majority of the operative procedures were conducted by the house staff, and our previous report [9] did not attribute improvement in mortality rate to increased operative experience. The 1940 to 1947 period has been marked by the institution of a five year residency system, and the majority of procedures have been carried out by assistant residents under supervision. Table 4 indicates the increased proportion of operations performed by the resident staff and the improved mortality rate for resident and attending staffs during the past eight years. The decrease in mortality cannot be ascribed to increased experience, as this covers the war years, when attending and resident staffs were depleted and the latter subject to

fluctuations in size and a rapid turnover of personnel. The fact that none of the deaths occurred during the war years 1942 to 1945 is evidence of the high standards maintained in the face of difficulties.

SEX AND AGE OF PATIENTS

During the 1940 to 1947 interval there was a lower proportion of male patients than formerly, caused, we believe, by the proportion of the male population in military service.

The age incidence by decade is presented in table 5. So much has been written about our aging population that this comparison of the preceding twelve years with the past eight years seems pertinent. It

TABLE 4.—*Comparative Mortality of the Resident and Attending Staffs.*

Period	Total Patients	Operated on by Residents	Percentage Total	Mortality Rate	Operated on by Attending Physicians	Percentage Total	Mortality Rate
1928 to 1939.....	677	410	60.5	3.4	267	39.5	7.8
1940 to 1947.....	265	237	89.4	1.2	28	10.6	3.5

shows that the majority of cases fall into the same age groups as formerly and dispels a clinical impression that an older group of patients with acute appendicitis is being seen.

HISTORY OF PREVIOUS ATTACKS

The most recent series agrees with the past review in that one fourth of the patients had had previous attacks of appendicitis.

TABLE 5.—*Incidence by Decades.*

	12 to 20	21 to 30	31 to 40	41 to 50	51 to 60	61 to 70	Over 70
1928 to 1939, %.....	30	33.2	16.6	11.5	5.1	1.1	1.0
1940 to 1947, %.....	29	32.7	14.7	11.3	6.0	4.5	1.8

DURATION OF SYMPTOMS

Table 6 shows the duration of symptoms in each classification during the three divisions of the twenty year study. We have been interested in this factor as an index of the influence of public health education as well as for its relation to mortality. It is significant at this time when education of the public is the keystone of the cancer control program. The effects of health education would probably be reflected more strongly among the population at large than in the segment served by Bellevue Hospital. However, our material indicates a progressive decline in duration of symptoms before treatment was sought by those patients with uncomplicated acute appendicitis and those with local peritonitis, the categories associated with the lowest

mortality. Furthermore, there is a progressive increase in the proportion of patients in these two groups. In the 1928 to 1933 interval 76.4 per cent of the patients had unperforated acute appendicitis or perforation with localized peritonitis, while 23.4 per cent had perforation with abscess or generalized peritonitis. The 1940 to 1947 interval shows that 92.4 per cent of the patients fell into the categories of uncomplicated acute appendicitis and localized peritonitis, while there were only 7.5 per cent with abscess and general peritonitis. These trends have been progressive and seem the most important factors in the decline in mortality.

CATHARSIS

In our previous report we drew no conclusions concerning cathartics as a factor in mortality. However, we have been interested in this problem also as an index of health education. From 1938 to 1939 cathartics had been taken by 26.1 per cent of the patients, whereas 18.4 per cent of the patients in the 1940 to 1947 series had taken cathartics. Only

TABLE 6.—*Duration of Symptoms.*

Diagnosis	1928 to 1933	Percentage	1934 to 1939	Percentage	1940 to 1947	Percentage
Acute appendicitis....	30 hr.	68.0	29 hr.	72.7	28 hr.	79.2
Local peritonitis.....	54 hr.	8.4	48 hr.	11.8	42 hr.	13.2
Abscess.....	5.6 days	17.6	10.2 days	6.6	6 days	4.5
General peritonitis...	52 hr.	5.8	56 hr.	8.7	74 hr.	3.0

1 of the 4 fatal cases in the later series was associated with catharsis. None of the patients of the 1940 to 1947 series had taken cathartics on the advice of a physician, a not uncommon finding in our earlier study. We cannot draw any conclusions regarding the decreased use of cathartics as a factor in the diminished mortality.

OPERATIVE PROCEDURES

The role of the McBurney incision in the reduction of mortality has not been so controversial since the advent of the antibacterial agents. It has become the policy to use this incision in the Fourth Surgical Division for all clearcut cases, reserving rectus-splitting incisions for questionable cases, especially those involving female patients. The McBurney incision has been used in such a manner as to obtain adequate exposure, and extensions medially or upward have been made as necessary to obviate the dangers of peritoneal and wound contamination associated with blind dissection and delivery of the appendical pathologic process. Table 7 summarizes our experience with the right rectus incision, while that with the McBurney incision is presented in table 8. The increased use of the McBurney incision has been accompanied with a decrease in the mortality rates. How-

ever, its actual role in this reduction cannot be accurately evaluated. Excellent surgeons and clinical observers [10] use rectus incisions with results comparable to those obtained with the McBurney incision. This leads us to believe that the latter may be given more credit for reduction in mortality than it actually deserves. The fact that the rectus incisions are used in patients presenting bizarre or complicated clinical pictures may weigh statistics falsely in analyses of case series. One patient of the 1940 to 1947 series who died was operated on through a right subcostal incision under the erroneous diagnosis of acute cholecystitis. This illustrates a point which we have previously

TABLE 7.—*Mortality When Right Rectus Incision Was Used.*

	1928 to 1933			1934 to 1939			1940 to 1947		
Diagnosis	No. of Cases	Deaths	%	No. of Cases	Deaths	%	No. of Cases	Deaths	%
Acute appendicitis	257	7	2.7	146	1	0.6	75	1	1.3
Local peritonitis	32	2	6.2	27	2	7.4	10	0	0.0
Abscess	64	6	9.3	13	1	7.6	2	0	0.0
General peritonitis	22	10	45.4	19	1	5.2	2	1	50.0
All forms of peritonitis	54	12	22.2	46	3	6.5	12	1	8.3

TABLE 8.—*Mortality When McBurney Incision Was Used.*

	1928 to 1933			1934 to 1939			1940 to 1947		
Diagnosis	No. of Cases	Deaths	%	No. of Cases	Deaths	%	No. of Cases	Deaths	%
Acute appendicitis	9	0	0	70	0	0	135	0	0
Local peritonitis	1	0	0	7	0	0	25	0	0
Abscess	5	0	0	5	0	0	10	1	10
General peritonitis	1	0	0	2	1	50	5	0	0
All forms of peritonitis	1	0	0	9	1	11.1	30	0	0

emphasized,[9] namely, that accurate diagnosis with direct approach to appendical damage is of more importance than the particular incision employed.

ABSCESS

The mortality rate for appendical abscess has remained approximately the same as in the previous study. The decline in the number of cases makes statistical comparison unfeasible. There were 12 patients with appendical abscess in the 1940 to 1947 period, 5 of whom were treated by drainage of the abscess alone. The patient who died was managed in this manner, but the cause of death was cardiac failure of rheumatic origin. Table 9 summarizes the results of management throughout

10. (*a*) Ladd, W. L., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941, chap. 15, pp. 220-229. (*b*) Lahey, F. H.: Technical Procedures Making Appendectomy for Gangrenous Appendicitis Safer, S. Clin. North America **22**:783-792 (June) 1942

the twenty-year period. It indicates that removal of the appendix is the better method of treatment. However, this is not correct, as drainage alone was selected for the more seriously ill patients and those in whom appendectomy presented technical difficulties. No patients have been treated by nonoperative measures.

DRAINAGE

Decrease in mortality rate is attributed to the decreased use of drains by Green,[6] Hoerr,[7] Jackson,[11] Meyer[4] and Schullinger.[5] Table 10 indicates the trend in this respect on the Fourth Surgical Division. Whether this decrease in use of drains has been a factor in the reduction in mortality or merely coincidental to it is still open to question. Our

TABLE 9.—*Management of Appendical Abscess (100 Cases).*

Procedure	No. of Cases	Percentage of Total	Deaths	Mortality Rate
Appendectomy	73	73	4	5.4
(Partial removal)	(4)	(6.2)	(0)	(0)
Drainage only	27	27	4	14.8
Totals	100	100	8	8.0

TABLE 10.—*Peritoneal Drainage as Part of Operative Procedure.*

	1928 to 1933		1934 to 1939		1940 to 1947	
Diagnosis	Number Drained	Percentage	Number Drained	Percentage	Number Drained	Percentage
Acute appendicitis	74	27.8	23	11.05	8	3.8
Local peritonitis	29	87.8	26	76.4	16	45.7
Abscess	68	98.5	19	100.0	12	100.0
General peritonitis	22	95.6	25	100.0	5	62.5

objection to drains has been the increased likelihood of obstruction of the small bowel during the postoperative period. There were 4 instances of such obstruction, with no deaths, among the last 265 cases, while there were only 2 cases, with 1 death, among the 677 patients studied over the 1928 to 1939 period. Our reduction in mortality seems to owe nothing to the decreased use of drains.

SULFONAMIDE COMPOUNDS AND ANTIBIOTICS

These agents have been used in 124 of the 265 cases from 1940 through 1947. We have tried many agents, combinations of agents and routes of employment. This varied use makes any attempts to compare small groups of cases undesirable. When intraperitoneal use of sulfanilamide crystals was so popular, this was used without untoward

11. Jackson, A. S.: Non-Drainage and Early Ambulation in Cases of Perforative Appendicitis, Arch. Surg. **54**:644-655 (June) 1947.

results. Since Meleney's [12] report in 1945, the use of this has been discontinued. During the past year the management of peritonitis with intravenous administration of sulfadiazine, massive doses of penicillin and streptomycin has become crystallized.

The paucity of complicated cases in the past eight years has not given a fair opportunity to judge the effectiveness of the antibacterial agents. The number of patients with abscess or generalized peritonitis is so small that statistical comparison with preceding years is impractical. There has been a decline in morbidity secondary to infection during the 1940 to 1947 period. There were no cases of subphrenic abscess, pylephlebitis or serious wound infections. The antibacterial agents have probably been a factor in this conspicuous improvement.

TABLE 11.—*Causes of Death.*

Cause of Death	1928 to 1939		1940 to 1947	
	Number	Percentage	Number	Percentage
Generalized peritonitis	27	77.0	1	25
Pylephlebitis	2	5.7	0	0
Subphrenic abscess	1	2.8	0	0
Postoperative hemorrhage	1	2.8	0	0
Shock	1	2.8	0	0
Obstruction of the small bowel	1	2.8	0	0
Postabortal hemorrhage	1	2.8	0	0
Rheumatic carditis	0	0.0	1	25
Mitral stenosis with decompensation	0	0.0	1	25
Hypertensive cardiovascular disease with failure	0	0.0	1	25

ANESTHESIA

Spinal anesthesia is cited as a major factor in the reduction of mortality by Schullinger,[5] Lahey,[10b] Meyer,[4] Hoerr[7] and Green.[8] Inhalation anesthesia has continued to be the anesthesia of our choice, spinal anesthesia being administered in only 16 of the 265 cases during the 1940 to 1947 interval. This proportion is approximately that of the preceding twelve years. This infrequent usage precludes spinal anesthesia as a factor in our reduction of mortality.

CAUSES OF DEATH

The causes of death from 1940 to 1947 as compared with those in the larger series of cases from 1928 to 1939 are presented in table 11. This illustrates the comparative decline of infection as a factor in mortality and the increased mortality associated with cardiovascular lesions. The latter observation has been previously noted by Green

12. Meleney, F. L.: A Statistical Analysis of a Study of the Prevention of Infection in Soft Part Wounds, Compound Fractures, and Burns with Special Reference to the Sulfonamides, Surg., Gynec. & Obst. **80**:263-296 (March) 1945.

and Watkins.[8] The decrease in deaths from postoperative generalized peritonitis is due primarily to the smaller number of late cases, although the sulfonamide compounds and the antibiotics may have played a role in its prevention in patients with perforation and localized peritonitis. Other factors in the reduction of mortality difficult to assess but nevertheless important components of present preoperative and postoperative care are improved methods of intubation, parenteral feeding and more rational fluid replacement.

Three of the 4 deaths in the 1940 to 1947 series have been of cardiac origin. The first occurred in a 28 year old nurse with a rheumatic background who suddenly exhibited pulmonary edema and died of cardiac failure on the second postoperative day after removal of an unperforated acutely inflamed appendix. Autopsy showed active rheumatic myocarditis and endocarditis with mitral stenosis and insufficiency. The second occurred in a 24 year old man previously treated for decompensation of rheumatic origin who was admitted in cardiac decompensation with an abscess of seven days' duration. After three days of unsuccessful effort at digitalization, during which the abscess increased in size, a McBurney incision was made over the mass under local anesthesia and 500 cc. of pus evacuated. Despite the melting away of the inflammatory mass the cardiac status became worse, and the patient died six days after operation. No autopsy was obtained. The third fatality involved a 62 year old man admitted with generalized peritonitis. After operation he did poorly, and he died of intraperitoneal sepsis on the thirteenth postoperative day. Autopsy confirmed the clinical diagnosis. The long survival is in contrast to the speedy death of patients with generalized peritonitis prior to the use of the antibacterial agents. The fourth death occurred in a 54 year old woman with severe hypertensive cardiovascular disease who was operated on under the erroneous diagnosis of acute cholecystitis. Exposure of the right upper quadrant showed a generalized peritonitis of appendical origin. Twelve hours after drainage signs of cardiac insufficiency suddenly developed and the patient died within an hour. Permission for autopsy was not obtained. This fatality has been mentioned to illustrate the role diagnostic errors and incorrect operative approach may play in mortality.

COMMENT

Comparison of this material with that of other authors indicates that the mortality rate has followed the general downward trend. However, not all the factors responsible for this improvement can be considered applicable in our study. The most important single factor in improvement has been the larger number of patients presenting themselves in the earlier stages of the disease. Our service has followed the general trend toward the McBurney incision and the decreased

use of drains but has not adopted spinal anesthesia. A word of caution is not out of place against attributing too large a role in the reduction of mortality to such factors as the use of the McBurney incision, spinal anesthesia and the decreased use of drains. It is possible that these factors may be coincidental with improvement rather than causative.

Our study indicates that employment of the sulfonamide compounds and the antibiotics has diminished complicating infections and reduced the deaths due to postoperative peritonitis. Their efficacy in cases of generalized peritonitis and abscess cannot be evaluated from this material because of the small number of cases. This phase of peritonitis will continue to present a changing picture as new agents are evaluated.

The increase in fatalities associated with cardiac complications draws attention to a problem that may become more general in the care of an older population. Two of our 3 patients who died from cardiac complications were in those categories associated with higher mortality rates. The efficacy of the antibacterial agents may preserve some of these patients long enough for them to succumb to a diminished cardiac reserve incapable of withstanding a protracted illness.

SUMMARY AND CONCLUSIONS

1. A survey of 952 cases of acute appendicitis and its complications during the twenty year period 1928 through 1947 has shown a progressive decline in morbidity and mortality rates.

2. The greatest single factor in the reduction of mortality has been the greater number of patients presenting themselves in the early stages of the disease.

3. Public health education and the increased alertness of the medical profession can be considered responsible for much of this improvement.

4. The sulfonamide compounds and antibiotics have contributed to the decrease in the deaths due to postoperative peritonitis and a diminution of complications secondary to infection.

5. The increased use of the McBurney incision and the decreased use of drains are not clearcut factors in our reduction of mortality.

6. In this era, when numerous advances in surgical care are contributing to lower mortality rates, it is difficult to evaluate the role of each one.

ANESTHESIA FOR OPERATIONS ON THE HEART AND GREAT VESSELS

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FOR MANY years surgery of the heart and the great vessels was confined to operations on the pericardium or to dramatic emergency procedures for the treatment of injuries, pulmonary embolism or cardiac arrest. Possibilities for further surgical intervention in this region were foreseen but reluctantly attempted.[1] Within the last decade, surgery of the heart and the great vessels has advanced tremendously. Operations have been attempted and successfully accomplished which would not have been deemed possible a relatively short time ago. The pathologic study of congenital heart disease and the correlation of anatomic defects with clinical symptoms by Abbott[2] instigated many of the surgical attempts to relieve some of these cardiac conditions. We believe that it is safe to say that these attempts might not have been so uniformly successful had not comparable advances been made in anesthesiology in recent years.

On Aug. 26, 1938 Gross[3] made the first successful closure of a congenitally patent ductus. The patient made a successful recovery. This operation is now performed by many.[4] Success with the pro-

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1. Elkin, D. C.: Emergency Surgery of the Heart, Am. J. Surg. **46**:551-561 (Dec.) 1939. O'Shaughnessy, L.: Future of Cardiac Surgery, Lancet **2**:969-971 (Nov. 4) 1934.

2. Abbott, M. E.: Congenital Heart Disease, in Nelson's Loose-Leaf Living Medicine, New York, Thos. Nelson & Sons, 1946, vol. 4, pt. 2, chap. 1, pp. 207-321.

3. Gross, R. E., and Hubbard, J. P.: Surgical Ligation of a Patent Ductus Arteriosus: Report of First Successful Case, J. A. M. A. **112**:729-731 (Feb. 25) 1939.

(Footnotes continued on next page)

cedure encouraged attempts to correct other defects of the heart and the great vessels. Soon followed successful operations on patients with coarctation of the aorta, double aortic arch, anomalous right subclavian artery and congenital pulmonary stenosis. These advances were outlined by Gibson.[5] In 1945 Crafoord,[6] having previously demonstrated on dogs that the circulation to all organs except the brain could be interrupted for as long as twenty-five minutes without organic damage, was able to perform an operation for coarctation of the aorta, completely removing the constriction portion. Gross,[7] also in 1945, reported the first operation for relief of a double aortic arch, which was constricting the trachea and the esophagus. Blalock's work in the treatment of pulmonary stenosis or congenital atresia of the pulmonary artery has saved the lives of many "blue babies" and advanced the hope of normal activity for them. His first paper, in which he described the anastomosis of a systemic branch (innominate or subclavian) of the aorta to the pulmonary artery in order to increase the circulation of the blood through the lungs, appeared in 1945.[8] His repeated success with this operation stimulated the extent of this treatment, to the benefit of many afflicted with the condition.[9] A modification of the Blalock procedure has been presented by Potts.[10] This consists of a direct anastomosis between the aorta itself and the pulmonary artery, made possible by the development of a special clamp to segregate a portion of the aortic wall for anastomosis without interfering with the general circulation at the time.

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4. (*a*) Gross, R. E.; Emerson, P., and Green, H.: Surgical Exploration and Closure of a Patent Ductus Arteriosus: Report of Second Successful Case, Surgery **6**:201-205 (Aug.) 1939. (*b*) Gross, R. E.: Surgical Management of Patent Ductus Arteriosus, Ann. Surg. **110**:321-356 (Sept.) 1939. (*c*) Blalock, A.: Operative Closure of the Patent Ductus Arteriosus, Surg., Gynec. & Obst. **82**:113-114 (Feb.) 1946.

5. Gibson, S.: Indications for Surgery in Congenital Cardio-Vascular Anomalies, Rocky Mountain M. J. **44**:459-461 (March) 1947.

6. Crafoord, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment, J. Thoracic Surg. **14**:347-361 (Oct.) 1945.

7. Gross, R. E.: Surgical Relief for Tracheal Obstruction from Vascular Ring, New England J. Med. **233**:586-590 (Nov. 15) 1945.

8. Blalock, A., and Taussig, H. B.: Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia, J. A. M. A. **128**:189-202 (May 19) 1945.

9. Blalock, A.: The Surgical Treatment of Congenital Pulmonary Stenosis, Ann. Surg. **124**:879-887 (Nov.) 1946; Physiopathology and Surgical Treatment of Congenital Cardiac Defects: Harvey Lecture, Bull. New York Acad. Med. **22**:57-80 (Feb.) 1946.

10. Potts, W. J.; Smith, S., and Gibson, S.: Anastomosis of the Aorta to the Pulmonary Artery: Certain Types in Congenital Heart Disease, J. A. M. A. **132**:627-631 (Nov. 16) 1946.

There have been sixty operations on the heart and the great vessels in our clinic in the past ten years. These operations fall into the following groups:

1. Partial pericardectomy	15
2. Ligation of patent ductus arteriosus	20
3. The Blalock or Potts' operation (for congenital heart disease with cyanosis or tetralogy of Fallot)	10
4. Operations on aneurysms of great vessels	6
5. Operation for mediastinal mass (near heart or great vessels and affecting same)	5
6. Operations for subacute bacterial endocarditis	2
7. Transthoracic cardio-omentopexy	1
8. Procedure for coarctation of the aorta	1
	60

It is almost self evident that the majority of patients suffering from serious malformations or diseases of the heart and closely related structures will be seriously ill. In many instances the circulation is so affected that the patient is suffering from cardiac decompensation or cyanosis or both. Many patients have infection superimposed on the defective areas. The exception to this surmise is often seen in patients with a patent ductus arteriosus. Frequently these young children are in good general condition, not having been affected by the complications of this condition which almost inevitably occur at least by the second or third decade of life.[4] These complications, subacute bacterial endarteritis and cardiac enlargement and decompensation, may be completely avoided if operative correction of the patent ductus is accomplished at an early age.[4] Since the likelihood of a patent ductus closing automatically after 1 year of age is negligible, operative intervention should be undertaken soon after this age.[4b, c] Thirteen of the 20 children in our series had no cardiac complications and were considered good risk patients. The other 7 had already suffered some cardiac damage; 2, in fact, had been in severe cardiac decompensation just previous to the operation.

The preoperative condition of our 60 patients with cardiac disease requiring surgical treatment is summarized in the table.

Patients' Condition Before Operation

Preoperative Condition	Good	Fair	Poor	Serious	Total
Pericarditis	..	6	5	4	15
Patent ductus arteriosus	13	4	1	2	20
Congenital heart disease	..	2	4	4	10
Aneurysm	..	3	3	..	6
Mediastinal mass involving heart	..	3	2	..	5
Endocarditis	..	..	1	1	2
Coronary disease	..	1	..	..	1
Coarctation of aorta	..	1	..	..	1
Totals	13	20	16	11	60

The youngest patient in this series was 18 months of age. This patient was suffering from an acute suppurative pericarditis. The oldest patient was a 56 year old man with an aneurysm of the innominate artery. The age classification of these patients by decades was as follows:

Years	Number of Patients
1 to 9	20
10 to 19	16
20 to 29	9
30 to 39	5
40 to 49	9
50 to 59	1

The condition in which these patients left the operating room is as follows:

As good as before operation or improved	46
Satisfactory	6
Fair	4
Poor	2
Died during operation	2

The 2 operative deaths are briefly summarized:

CASE 1.—A 37 year old man with subacute bacterial endocarditis of several years' duration was operated on. The anesthesia was ethylene-oxygen and ether with positive pressure oxygen-ether when the chest was open. The operation involved opening of the left ventricle and removal of vegetations from the heart valve. The heart was being closed with two mattress sutures when a coronary vein became occluded with a small piece of the dislodged vegetation, and cardiac arrest immediately followed. The heart was directly stimulated and massaged, and its activity was temporarily restored. However, the cardiac arrest recurred, followed soon by respiratory arrest, and although 100 per cent oxygen was given with artificial respiration and cardiac massage was repeated, all further attempts at resuscitation failed to restore life.

CASE 2.—The second patient was a 5 year old boy with congenital pulmonary stenosis who was cyanotic and underdeveloped. The diagnosis was tetralogy of Fallot. The anesthesia was oxygen and ether. A Blalock operation was under way. After mobilization of the left pulmonary artery and partial mobilization of the left subclavian artery the patient exhibited a marked slowing of the pulse, closely followed by complete cardiac inhibition. There was no response to cardiac massage, stimulants or intermittent positive pressure oxygen and artificial respiration. It was concluded that this death was due to an insufficient pulmonary circulation with an open chest in a patient in whom the aeration of the blood was already markedly impaired by his congenital cardiac defects.

In this series of 60 patients there were 4 postoperative deaths. Two of these were in the pericardectomy group. One patient died three weeks after pericardectomy of polyserositis and cardiac failure due to obstruction of pulmonary veins by the pathologic process. The second patient died seven months later of pulmonary tuberculosis, which had been present preoperatively but seemed to be reactivated after the pericardectomy.

In the group who were subjected to a Blalock operation there was 1 postoperative death. The patient was a 6 year old boy who was apparently making a satisfactory recovery from the operation but suffered a cerebral embolism three weeks postoperatively, with resulting hemiplegia followed by increasing mental deterioration and death several weeks later. The tendency to cerebral embolism is marked in this condition of pulmonary atresia, since there is increased viscosity of the blood due to the polycythemia which develops in all the patients in the attempt to carry more oxygen to the oxygen-starved tissues.

The other postoperative death involved a patient with an aortic aneurysm which had been explored under local anesthesia. This patient died from rupture of the aneurysm and fatal hemorrhage one week following operation.

Aside from the death in the Blalock group the only other complication in this group was paralysis of the left side of the diaphragm in 1 patient. This paralysis was not particularly discomforting to the patient, and recovery occurred after six weeks.

The complications after ligation of the patent ductus were more numerous, but none was particularly severe. Two patients had an infection of the upper respiratory tract with fever and cough shortly after operation. Both recovered in a few days. One had atelectasis of the middle lobe of the left lung with a high fever. This was corrected with medical management and positive pressure oxygen inhalations. Bronchoscopy was not necessary in this patient. Two had tachycardia lasting a few days, and in 1 hypertension developed and then subsided spontaneously within a week. One patient had an unexplained high fever lasting twenty-four hours, 1 had retention of urine requiring catheterization for thirty-six hours, 1 had severe nausea and emesis lasting three days and 1 had a pleural effusion.

The postoperative complications of the pericardial operations, aside from the 2 fatalities mentioned previously, were as follows:

Oxygen want (longer than twenty-four hours)	3
Lobar pneumonia	1
Tachycardia	1
Auricular fibrillation	2
Moderate postoperative hemorrhage	1
Severe postoperative hemorrhage	1
Severe secondary anemia	1
High fever	2
Distention	1
Infection of the wound	1

The anesthetic agents and combination of agents used in these sixty operations are next listed. All patients were given some degree of positive pressure oxygen or oxygen with a gaseous anesthetic agent through a tight-fitting face mask when the chest was open. The

amount of positive pressure employed varied with each patient, their oxygen requirements, their general reaction and the visual appearence of the lung and mediastinum when the chest was open.

Ethylene-oxygen plus ether	29
Vinyl ether-ether induction by open drop; ether-oxygen when chest was open	13
Ethylene-oxygen	6
Nitrous oxide-oxygen plus ether	6
Local infiltration plus oxygen	5
Ethylene-oxygen plus thiopental sodium ("pentothal sodium") intravenously	1
Total	60

Harmel and Lamont [11] and many others have successfully used cyclopropane-oxygen in a high percentage of their patients with cardiac disease. We have avoided the use of this agent in our cardiac operations because of its questionable effects on heart action and vagal reflexes. This will be discussed later.

GENERAL MANAGEMENT

Preoperatively the patient with cardiac disease is thoroughly studied and his general condition is improved as much as possible. Vitamins and penicillin are usually given before the day of operation. Vital capacity is determined. Sometimes oxygen is administered for several days. We endeavor to give enough preoperative medication to allay apprehension yet avoid oversedation and overdepression of reflexes, as occasions may arise during operation when this may make a difference between life and death. It is easier to arouse a patient from an anesthetic dose of ether than from an excessive dose of morphine. Heavy premedication may delay the awakening period after the operation. We consider this particularly undesirable after surgical intervention for cardiac disease. The young children with congenital defects of the heart have received no premedication at all in most instances. Excitement during induction can be avoided for the most part by winning the confidence of the child and carefully administering vinyl ether or gas. We have preferred to do this rather than complicate the picture with premedicants. Mucus secretion is minimized by a smooth induction period. Suction aspiration is employed whenever indicated, and the thinner the secretion the more quickly and completely it can be removed.

During operations on the heart, the anesthesiologist must cope with the effects and possible complications of an open chest, open mediastinum and direct operative manipulation of the heart and the great vessels. He must be able to control ventilation adequately in these circumstances and yet keep the structures relatively quiet so that the surgeon's

11. Harmel, M. H., and Lamont, A.: Anesthesia in the Surgical Treatment of Congenital Pulmonic Stenosis, Anesthesiology **7**:477-498 (Sept.) 1946.

work will not be too difficult. He must continually bear in mind the effects that the open chest and the operative procedure may have on the respiration and the circulation and be able to deal with any complications which may arise.

The open chest alters pressure relationships, the exchange of gases, respiratory rhythm and the circulation of the blood. There is a diminution of tidal volume, and the patient must compensate by an increase in the rate or amplitude of respiration or the anesthetist must do the compensating by increased pressure and increased oxygen content of the gases reaching the alveolar spaces. There must be more inhalation pressure, particularly of oxygen, entering the lung through the trachea than air through the pneumothorax outside the lung. It must be remembered that the lung on the opposite side may also be affected, for unless the mediastinum is rigidly fixed by adhesions, a pneumothorax on one side is also bound to affect the opposite lung to some degree through movements of the mediastinum and the effects of the change of mediastinal position on the vagi. If the vagal stimulation by a collapsed lung and operative disturbances causes an increase in the rate and depth of respiration, it may be a good thing for the patient, but it does not contribute to a quiet operative field. Adequate ventilation must be maintained without overactivity of the respiratory movements. Mediastinal shift or flutter, due to unequal pressures in the chest cavities, may cause a tear in the pleura of the opposite side resulting in bilateral pneumothorax.

The lack of sufficient gaseous exchange between the alveolar content and the circulating blood, particularly inadequate oxygenation of the blood, must be corrected by providing adequate inhalation pressure along with an increase in the oxygen concentration delivered to the alveoli in order to provide an adequate oxygen intake. This increased inhalation pressure will also tend to make respiratory movements quieter and thereby facilitate the technical procedures of the operation. Should paradoxic respiration (a sucking in of the chest during inspiration) occur in the unopened side of the chest, it also may be corrected by an increase in the inhalation pressure, provided the patient's airway is clear and patent. If an intratracheal tube is in place, one must be certain that it is clear of any secretions and also that it is of adequate bore to assure a good respiratory exchange. If these precautions are not observed, paradoxic respiration may occur in the unopened side. It is dangerous to the patient to allow too much atelectasis to occur in the exposed lung or any degree of atelectasis to exist for a long period, as it must be remembered that if blood continues to circulate through these atelectatic areas, it returns to the general circulation without receiving the necessary oxygen. Adding a volume of unoxygen-

ated blood to the general circulation of a patient already suffering from oxygen want may be disastrous. If the pulmonary artery on the exposed side is completely occluded during the procedure, any existing atelectasis will not be so detrimental, as blood aerated from the other lung may suffice for this period. As long as the exposed lung is receiving blood from the heart, it should be kept well aerated.

If pulmonary ventilation is not adequate, carbon dioxide may accumulate rapidly, so the respiratory exchange must be ample enough to eliminate excess carbon dioxide as well as to provide the needed oxygen.

A collapsed lung tends to set up a prolonged inspiratory effort. On the other hand, forcible overdistention of the lungs with positive pressure results in a prolonged expiratory effort.[12] Therefore, both inhalation and exhalation pressures must be adjusted to combat these deleterious tendencies. At this stage of the surgical procedure the visual appearance of the lung and mediastinum will also be a guide in the adjustment of pressures. Generally, the inhalation pressure necessary is somewhere between plus 6 and plus 15 mm. of mercury and the exhalation pressure between plus 2 and plus 5 mm.

The circulatory effects of an open chest are in part due to a venous stasis, i. e., a slowing of the venous return to the heart and a steadily rising venous pressure.[13] More serious effects may be produced by vagal stimulation causing irregularities of the cardiac action as well as irregularities of the respiration. The stimulation of the vagi may inhibit the normal pacemaker and force other centers to take over this function, resulting in a slow irregular rate.[14] This theory does not explain all the irregularities which may occur. Some may be due to the mechanical effects of the operation or to the pneumothorax alone. Some may be due to the anesthetic agent through its action on the myocardium itself or on the coronary vessels nourishing the myocardium or perhaps by the effect of the anesthetic on vagal reactions.

All these considerations must be borne in mind in choosing an agent, method and technic for operations on the heart. We have preferred to adopt a relatively standard method of caring for these patients, varying it somewhat according to individual factors, such as the age of the patient, his general condition and the necessary management of

12. Head, H.: On the Regulation of Respiration, J. Physiol. **10**:1 and 279, 1889.

13. Sauerbruch: Zur Pathologie des offenen Pneumothorax und die Grundlagen meines Verfahrens zu seiner Ausschaltung, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **13**:399-482, 1904.

14. Beecher, H. K.: The Circulation and Anesthesia, in The Physiology of Anesthesia, New York, Oxford University Press, 1938, pp. 157-217.

complications as they may arise. We feel that the anesthetist himself may better perfect his own technic by using a standard method. It naturally follows that the more efficient and understanding the anesthetist becomes, the safer is the patient in his hands. We preferred to use an agent which would be least harmful physiologically to the respiratory and cardiac mechanism, choosing one which is essentially stimulating rather than depressing to these functions. The agent must be potent in the presence of high percentages of oxygen invariably required when the chest is open. We also felt that the agent used should not contraindicate the use of any cardiac or respiratory stimulants, should indication for their use arise.

The method should provide the best possible ventilation of the alveolar air spaces and keep the anesthetic "dead space" at a minimum since any increase in this subtracts from the tidal volume, which automatically becomes diminished in the presence of an open chest. The technic should be as simple and as free of potential complications and hazards as possible, and the periods of anesthetic induction and recovery should be reduced to a minimum in order that the anesthetic time should not too greatly exceed the operative time. Above all, the patient should be awake before returning to his bed. The presence of active reflexes and cooperation on the part of the patient preclude various hazards otherwise present during the periods of unconsciousness or awakening.

In line with this reasoning we chose ether as the chief anesthetic component for the majority of patients. Ether, after induction with vinyl ether, ethylene-oxygen or nitrous oxide–oxygen, was administered during the maintenance period with oxygen, or gas-oxygen if the patient's oxygen requirement permitted it, and with positive pressure when the chest was open. A tight-fitting face mask was employed throughout. We have not felt justified in the use of cyclopropane because of the cardiac irregularities which this agent may in itself produce or render the heart more sensitive to under other conditions which are apt to be present during operations on the heart. The further tendencies of cyclopropane to slow the pulse, depress the respiration and accentuate vagal reactions have made us hesitate to use this drug. The method by which cyclopropane must be given has also contraindicated its use in our minds, since the "closed" system necessarily increases the anesthetic "dead space" so that tidal volume must be increased in order to wash out the alveolar spaces adequately. Although we do not make routine or even frequent use of any analeptic drugs during these operations, an occasion may arise when the need is present for stimulants in addition to intravenously administered fluids

and blood. So many stimulants are contraindicated under cyclopropane [15] that we prefer not to use this agent.

The increased loss of body heat from an open chest [15] must be borne in mind as an additional factor in the contribution to the occurrence of shock. Actually we have not encountered shock as frequently in operations on the heart as in procedures involving the lungs or even the abdomen. The operations are usually not too long, and the loss of blood is comparatively small unless hemorrhage unexpectedly occurs. In fact, in cases of congenital cardiac defects and of cardiac decompensation from any cause care must be taken not to overload the circulatory system with fluids. Still, the possibility of the occurrence of shock is always prepared for by introducing a needle or cannula into a vein in the ankle and being ready to give fluids and blood. Usually isotonic sodium chloride solution or plasma is administered slowly, and the speed of the intravenous infusion can be increased at a moment's notice. The patient is always typed, and blood is prepared and kept at hand for transfusion.

Postoperatively, oxygen is administered for at least twenty-four hours and longer if necessary. A tent is used for young children and nasopharyngeal insufflation for older children and adults. A machine for administering mask oxygen under positive pressure is kept at the bedside for at least twenty-four hours after operation, ready for instant use should an emergency situation arise. A patient showing any degree of oxygen want in the immediate postoperative period is accompanied to his room by the anesthetist, who administers oxygen en route. This obviously includes all patients who have undergone operations for congenital pulmonary atresia.

CATHETERIZATION OF THE HEART

In addition to the sixty operations mentioned previously, we have had sixteen diagnostic catheterizations of the heart conducted in the fluoroscopic room.

Catheterization of the heart was performed as early as 1889 by Nicholas Senn,[16] who catheterized the right side of the heart in animals

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15. Waters, R. M.: Present Status of Cyclopropane, Brit. M. J. **2**:1013, 1936. Meek, W. J.; Hathaway, H., and Orth, O. D.: The Effects of Ether, Chloroform, and Cyclopropane on Cardiac Automaticity, J. Pharmacol. & Exper. Therap. **61**:240-252 (Nov.) 1937. Allen, C. R.; Stutzman, J. W., and Meek, W. J.: The Production of Ventricular Tachycardia by Adrenalin in Cyclopropane Anesthesia, Anesthesiology **1**:158-166 (Sept.) 1940. Evans, W. E.; Oster, R. H., and Krantz, J. C.: A Comparative Study of Propethylene and Cyclopropane on Cardiac Automaticity, J. Pharmacol. & Exper. Therap. **83**:40-44 (Jan.) 1945.

16. Senn, N.: Experimental Surgery, Chicago, Chicago Medical Book Co., 1889, pp. 268-269.

to aspirate air emboli, produced experimentally. He introduced a catheter into a jugular vein and passed it to the right auricle and was able on several occasions to remove air emboli, thus preventing a fatality in the animal. Forssmann [17] employed this procedure clinically in 1929, his first subject being himself. Cournand and Ranges [18] in 1941 utilized this procedure to measure the cardiac output and to collect blood samples from the right auricle. By use of the catheter, samples of blood may be withdrawn from various sites for determination of its oxygen content or for other studies and mean pressures of blood flow may be measured.

The anesthetic management of patients presented for this procedure differs considerably. Since the procedure involves little sensory stimulation, local anesthesia or basal narcosis supplemented with local anesthesia is usually adequate. It has been our practice to induce the anesthesia in these patients, who have been children under 14 years of age, in their rooms with either tribromoethanol solution or thiopental sodium given by rectum. Induction in the patient's room has a decided advantage over induction in the fluoroscopic room because the child is less apprehensive and more cooperative there and as a result induction is more rapid and profound. Mask oxygen and suction equipment are available but kept just outside the room since the presence of these mechanical devices oftentimes excites the patients, particularly the younger ones. It is our routine to approach the patient with only the rectal catheter and the "asepto" syringe containing the previously mixed anesthetic solution. A "placebo" enema is given to the extremely excitable patients on one or two mornings before the catheterization in order to gain their confidence. After induction the patient is transferred in his bed to the fluoroscopic room.

In our hands, tribromoethanol solution given rectally seems to produce a more profound narcosis than does thiopental sodium by the same route, and the duration of the narcosis is longer. Preoperatively the patient receives no medication except atropine, which is administered only when thiopental sodium is to be used. A cleansing enema of isotonic sodium chloride solution is routinely given the evening before operation, and all the patients, of course, are accurately weighed to compute the dosage of the basal rectal anesthesia. The dosage of tribromoethanol solution for the average patient is 100 mg. per kilogram of body weight. We have never had occasion to supplement or repeat

17. Forssmann, W.: Die Sondierung des rechten Herzens, Klin. Wchnschr. **8**:2085-2087 (Nov. 5) 1929.

18. Cournand, A., and Ranges, H. A.: Catheterization of the Right Auricle in Man, Proc. Soc. Exper. Biol. & Med. **46**:462-466 (March) 1941.

the dose during the procedure. For the dose of thiopental sodium by rectum, we use 1.0 Gm. per 50 pounds (22.7 Kg.) of body weight. Infrequently, a supplemental dose of the thiopental sodium is necessary during the procedure, particularly if it is of long duration.

Procedure.—The previously anesthetized patient is placed on the fluoroscopy table in the supine position with the right arm extended and bound securely to an armboard. The arm is prepared and draped, the usual sterile technic being used. A tourniquet is placed above the right elbow, and the basilic vein is palpated. An area immediately superficial to the vein is infiltrated with a 1 per cent procaine solution, and a transverse cut-down is accomplished. When the basilic vein is identified the tourniquet is released, a small incision is made into the anterior wall of the vein and the distal portion of the vein is ligated. A special plastic catheter, to which is connected a 500 cc. flask of isotonic sodium chloride solution, is then introduced into the proximal portion of the vein and the flow of this solution regulated to 35 to 40 drops per minute. At this point the fluoroscopy screen is adjusted over the upper part of the thorax and the room is darkened. The catheter is introduced slowly by the operator, finding its way into the axillary and subclavian veins. About the time the catheter passes into the subclavian vein the tip of it can be identified on the screen of the fluoroscope and its subsequent movement into the innominate vein, superior vena cava, right auricle and right ventricle can be followed visually. Entrance into the right pulmonary artery is difficult.

Blood samples are withdrawn from the right ventricle, right auricle and superior vena cava simply by attaching a prepared syringe to the distal end of the catheter and slowly withdrawing the catheter and identifying its position on the screen of the fluoroscope.

After the samples are taken, the catheter is removed entirely from the vein and the incision sutured. A sample of arterial blood is then drawn from the femoral artery, and the procedure is complete. These blood samples are analyzed for oxygen content.

During the operative procedure the anesthetist closely watches the patient's condition and assures a patent airway. An oral airway is always introduced, and this usually is sufficient if the chin is moderately extended or the mandible is supported anteriorly. Infrequently the patient becomes restless toward the end of the procedure, particularly if the effects of the procaine around the catheter have worn off.

Oxygen and suction should be available, and the anesthetist should take adequate measures to protect his hands from the rays of the fluoroscopy screen.

SUMMARY

A survey of 58 cases in which sixty intrathoracic operations on the heart or great vessels have been performed is presented and the results summarized. There were 4 postoperative deaths and 2 deaths in the operating room, making a total mortality rate of 10 per cent. The causes of postoperative death were polyserositis and cardiac failure (1), pulmonary tuberculosis (1), rupture of an aortic aneurysm (1) and cerebral embolism (1). The 2 deaths during operation were due to (1) coronary occlusion and (2) anoxia and cardiac failure due to insufficient pulmonary circulation with an open chest in a patient with congenital pulmonary stenosis.

The preoperative preparation, the anesthetic management and the postoperative care of the patients are discussed.

A brief review of the management of patients in the diagnostic procedure of cardiac catheterization is also presented.

PENETRATING ABDOMINAL WOUNDS

With Special Reference to Operation in the Presence of Shock

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AT THE Homer G. Phillips Hospital, a St. Louis city institution exclusively for the care of sick and injured Negroes, 134 consecutive cases of traumatic wounds of the abdomen were observed between January 1940 and January 1946, inclusive. Almost half of the patients, or 66, were operated on, and a wound was found which had penetrated a viscus. This is exclusive of 1 patient who died within twenty minutes of admission to the hospital and 29 operated on in whom perforation of a viscus was not found. Of the patients whose case was analyzed, 21 were in shock on admission and will be discussed more fully. The majority of the wounds were inflicted by stabbing (99 cases of 134). Since the depth of stab wounds is frequently limited, it is likely that such wounds tend to be less severe than those inflicted by firearms. Wounds from high-powered firearms frequently seen in the armed services were not encountered.

GENERAL CONSIDERATIONS

For the proper evaluation of our material, certain general considerations should be emphasized.

Time Interval.—The time elapsing between injury and the institution of therapy has long been known to be an important factor in the outcome of the case. This was true in our cases, as shown in table 1.

The length of this interval depended in part on the speed with which patients were dispatched by the city ambulance service to the hospital. Inasmuch as ambulance and patrol service was always available, the average length of time consumed in conveying the patients to the hospital after injury was seventy-eight minutes. More than 75 per cent of them arrived at the hospital within thirty minutes after injury. The shortest time was ten minutes and the longest fourteen hours. There were, however, exceptional cases in which patients arrived at the hospital several hours after injury. This may have been due to an

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attempt to elude the police or the failure to recognize the severity of the condition.

Delays in operation other than those mentioned were due to inability to obtain permission to operate immediately and to the need for further clinical investigation or preoperative preparation.

Care of Patients in Shock.—All surgeons are often faced with the problem of when to perform an emergency operation on a patient already in shock due to a lesion the correction of which requires surgical intervention. To operate on such a patient with the shock uncorrected is obviously hazardous; yet there is an equal hazard should there be a delay in operation to correct the cause of the shock, particularly when the passage of time permits the patient to enter the irreversible stage of shock. In no other situation is this problem more apparent than in cases of penetrating abdominal wounds. For this reason special attention was given in this study to such cases.

TABLE 1.—*Length of Time Before Operation, with Mortality*

Hours	Number Operated on	Number Who Lived	Number Who Died	Mortality, %
0 to 1	18	16	2	11.1
1 to 2	42	36	6	14.3
2 to 4	22	17	5	22.7
4 to 6	9	7	2	22.2
Over 6	4	2	2	50
	96	78	17	

In the present series, 21 patients were in shock on their admission to the hospital. The diagnosis of shock was made when the blood pressure was 100 systolic and 70 diastolic or lower on repeated measurements and when the symptoms and signs such as apprehensiveness, restlessness, cold and clammy skin, dulled sensorium, rapid feeble pulse, cyanosis and oxygen starvation were present. The patients were carefully studied for purposes of discussion and divided into the following four groups:

1. Four patients were classified as suffering from neurogenic shock, because at operation little, if any, bleeding was found, although all had perforations. It is probable that tissue trauma was partly responsible for the shock, though added factors were undoubtedly important, such as excessive fright, pain and acute alcoholism. It is noteworthy that in these cases the blood pressure frequently fell to such low levels as 40 systolic and 0 diastolic. In general, the patients responded to therapy within fifteen to sixty minutes, which included the administration of 1,000 to 2,000 cc. of 10 per cent dextrose, mild sedatives and analgesics. All these patients recovered.

2. Ten patients classified as being in hemorrhagic shock included those who had lost between 500 to 1,500 cc. of blood. In spite of the large loss of blood, these patients recovered, although all but 3 received inadequate replacement of the blood volume, which was due mainly to the fact that no blood was available. Since the establishment of a blood bank at this hospital, larger quantities of blood and plasma are being used. In addition to dextrose, 4 patients received 500 cc. of plasma, 2 received 500 cc. of plasma and 500 cc. of whole blood, 1 received 1,000 cc. of plasma, 1 received 1,000 cc. of whole blood and 2 received 2,000 cc. of whole blood and 1,000 cc. of plasma on the operating table while the operation was delayed.

3. Two of the patients who died did not die of shock. Both survived operation but died of uremia and peritonitis after forty-five and twenty-one days, respectively.

4. The remaining 5 patients died in shock, and their deaths are therefore classified as probably preventable, in that it is believed that if adequate replacement had been effected and adequate operative treatment given at the proper time, death might have been avoided. One patient received no blood and another but 500 cc. of plasma and 500 cc. of whole blood because no more was available at the time, yet both of these had sustained extensive intra-abdominal trauma, with a loss of blood estimated between 1,000 and 1,750 cc. The third patient received 1,500 cc. of blood and 1,500 cc. of plasma but died on the operating table from loss of blood through a rent in the inferior vena cava. More prompt recognition of this injury might have prevented this death. In the remaining fatal cases there was extensive and uncontrollable loss of blood into the pulmonary parenchyma and the pleural cavity.

In considering the problem of when to operate in the presence of shock, attention should be focused on these 5 cases. In the first 2, in which a large amount of blood had been lost, death could undoubtedly have been prevented had more blood been available to replace the loss. Yet most of the 10 patients who recovered received inadequate transfusions. The question might then be asked: How does one know when adequate blood replacement is crucial and when it has been effected? On the basis of past experience, operation should be prepared for at once if patients who have not responded to antishock measures in thirty minutes are not moribund. At operation bleeding vessels are promptly located and the bleeding controlled. The amount of hemorrhage is estimated and the blood rapidly replaced, positive pressure being used and several veins, if necessary. Further operative procedures are then delayed while the circulation is restored. Two such patients were included under the classification of hemorrhagic shock with recovery.

Even if the hemorrhage is from a major abdominal vessel, the same procedure should be practiced. One case fell into this category in that the vena cava was torn. It was included under the classification of preventable deaths only because larger quantities of blood were not then available. The patient was given 500 cc. of whole blood, 500 cc. of plasma and 1,000 cc. of 5 per cent dextrose, without improvement. He was operated on within ninety minutes, and 1,000 cc. of whole blood and 1,500 cc. of plasma were administered on the operating table. This, however, was not enough, in view of the great loss of blood (3,000 to 4,000 cc.) due to extensive injury to the inferior vena cava, the hilus of the kidney, the spleen and the pancreas. It seems clear that had more blood been given, this death might have been prevented. It was striking that in this patient, in whom extreme exsanguination and extensive intra-abdominal damage had occurred, the blood pressure was restored to 100 systolic and 50 diastolic and the circulation maintained for four hours despite the anesthesia and a major operative procedure.

Diagnosis.—The diagnosis in the cases under discussion was sometimes difficult to establish, especially in cases in which the wound of entry was a considerable distance from the abdomen. Any gunshot wound between the seventh rib and the upper third of the thighs was considered to have penetrated the abdomen unless it was proved otherwise. Diagnosis was seldom difficult when there was a wound of entry and a wound of exit. A careful history, a complete physical examination and roentgenologic studies were important adjuncts in the determination of adequate therapy.

When there was doubt as to whether penetration into the abdominal cavity had occurred, the abdomen was always explored, either by opening it through an incision separate from the traumatic wound or by incising or excising the existing wound. For the most part the first procedure was used; the latter was carried out in only 12 cases and had the merit of sparing the patient the more major procedure of opening the abdominal cavity.

Roentgen examination was seldom used except for patients in whom there was no wound of exit or in whom the wound of entrance was distant from the abdomen. The following case illustrates its value:

A. C., a 38 year old woman, entered the hospital with a history of having been shot in the right side of the chest thirty minutes previously while lying in bed. There were symptoms of thirst, dyspnea, pain in the right lower side of the chest on deep inspiration and pain in both lower abdominal quadrants (present prior to injury). There was a history of a profuse vaginal discharge prior to the present menstrual period, which began two days before her admission.

The temperature was 97 F., the pulse rate 98 and the respiratory rate 28. The blood pressure was 110 systolic and 60 diastolic. Positive findings included a 1.5 cm. puncture wound in the fourth interspace of the anterior region of the chest in

the midclavicular line, a small pneumothorax involving the right side and abdominal tenderness at the right costal margin and in both lower quadrants. Vaginal examination revealed tenderness and fluctuation in both adnexa.

Roentgenologic examination of the abdomen showed a medium caliber bullet lodged in the ileum, on the right side.

Immediate laparotomy revealed a laceration of the right half of the diaphragm, a through and through laceration of the right lobe of the liver, six perforations of the small bowel and perforation of the right broad ligament with active hemorrhage from the ovarian vessels.

Had not the roentgenograms revealed the site of the bullet, the presence of intra-abdominal injury might have been mistaken for preexisting pelvic inflammatory disease. It is probable also that it could have been ascertained without the aid of the roentgen examinations that there was intra-abdominal trauma if the history had been obtained that the gun had been fired from a position above the patient's head while she was supine and had the proper evaluation of the finding of powder marks at the upper pole of a groovelike wound been made.

THERAPEUTIC PROCEDURES

Emergency Measures.—In the emergency room all patients received 1,500 international units of tetanus antitoxin and a limited examination. Wounds were not probed, nor was any attempt made to determine the full extent of injury. Ward physicians and nurses were notified of the case immediately. Transfer of the patient from the emergency room to the ward usually consumed not more than five minutes. In the ward necessary emergency measures were instituted and typing and cross matching done.

Preoperative Treatment.—Except for the ordinary preoperative preparation of the patient, no therapy was given except in cases in which the patients entered the hospital in shock. This preoperative therapy has already been discussed in detail.

Anesthesia.—In the selection of an anesthetic, each case was considered individually. In the uncomplicated cases, which comprised 70 per cent, spinal anesthesia (simple spinal anesthesia in 50 per cent and continuous spinal anesthesia in 20 per cent) was used. The relaxation so obtained was a great aid in examining the abdominal contents completely. However, spinal anesthesia was not used for uncooperative patients, intoxicated patients, obese patients, patients with combined thoracoabdominal wounds or patients with persistently low blood pressure. For such patients ether and cyclopropane were employed more frequently when general anesthesia was necessary. In a few instances in which spinal or local anesthesia proved inadequate, a supplemental general anesthetic was necessary.

Operative Measures.—Preparation of the skin was performed in the usual manner except when a viscus was protruding, in which case the protruding organ was protected while the skin was cleansed. The protection was then removed and the wound and the prolapsed organ irrigated with copious amounts of isotonic sodium chloride solution. The type of incision varied considerably with the type of wound. In most instances, a mid-rectus incision was made, away from the primary traumatic wound. When the wound was large, débridement of the edges was sometimes done and the abdomen entered through the wound. At times it was necessary to enlarge the original incision for adequate exposure.

At operation the first aim was to control active hemorrhage, it being kept in mind that the most frequent sites of massive intra-abdominal hemorrhage are mesenteric and omental vessels, solid viscera (liver, spleen and kidneys) and the great vessels. After active hemorrhage had been controlled, exploration of the organs was done in the following order: large bowel, small bowel from the ligament of Treitz to the ileocecal junction, stomach, liver, spleen, bladder and retroperitoneal viscera.

Management of Injuries to Specific Organs.—1. Blood Vessels: Extensive injury to the aorta, inferior vena cava and iliac vessels usually resulted in rapid death. Hemorrhage from smaller vessels (mesenteric, celiac and omental) was most often seen. Mechanical suction, the use of large abdominal tapes and manual hemostasis allowed visualization of the bleeding points so that they could be ligated. If it was necessary to ligate large mesenteric vessels to control hemorrhage, it was important to determine if the bowel they supplied was viable. This was done by determining the size and the degree of anastomoses of the involved vessels and by noting the change in color of the bowel under stimulation with warm compresses. These vessels were ligated, since the thrombi might have been dislodged during manipulation of the bowel.

2. Diaphragm: The importance of recognition of perforations of the diaphragm and their closure by suture cannot be overemphasized. The immediate danger is massive pneumothorax or hemothorax, while later complications include pleural infection and diaphragmatic hernia. The greatest difficulty we encountered in suturing diaphragmatic perforations was in obtaining adequate exposure. This was usually overcome by ample extension of the incision.

3. Stomach: In general, wounds of the stomach offered few problems. In all cases of injury to the anterior surface it was necessary to expose the posterior surface, either by direct visualization of the interior through the anterior wound or by exposure of the lesser peritoneal

cavity to look for evidence of injury. In several cases undigested food particles had escaped into the free peritoneal cavity; as much as possible was removed.

4. Large and Small Bowels: Thorough and meticulous inspection of the bowel was done. The following signs sometimes aided in the recognition of intestinal perforations: eversion of the punctured mucosa, escape of gas and/or fluid, dark brownish discoloration of the adjacent bowel and the presence of crepitation in hematomas at the mesenteric borders. A missed intestinal perforation almost invariably results in peritonitis and death. It is well to remember that unless a gunshot wound is tangential or unless the missile is within the lumen of the intestine, there should be an even number of perforations. In this series, Lembert or Cushing sutures were used to effect inversion. Narrowing of the lumen, especially in perforations of the small bowel, was avoided by directing the suture line across the long axis of the lumen. In 6 of our cases the small bowel was so traumatized that resection was necessary. In 2 other cases resection was done because the blood supply to the bowel was compromised. The exteriorization of perforations of the large bowel, frequently recommended in military practice, was not employed.

5. Gallbladder: Two cases of perforation of the gallbladder were encountered, and suture was readily carried out. If there had been widespread damage to the gallbladder or its blood supply, cholecystectomy would have been performed.

6. Spleen: Though the spleen is a solid viscus, suturing, even of minor lacerations, may result in further bleeding. For this reason, splenectomy was performed in all cases of laceration of the spleen. The use of hemostatic preparations such as gelfoam® (absorbable gelatin sponge) or oxycel® (an absorbable oxidized cellulose) may alter this procedure.

7. Kidney: In cases of extensive lacerations of the kidney, especially if the renal vessels were involved, nephrectomy was done. In instances of less extensive lacerations the kidney was left intact. When injury to the kidney is apparent, it is important to evaluate the injury carefully by adequate exploration of the organ. In 2 of our cases minor lacerations with small retroperitoneal hematomas did well without nephrectomy. It is obvious that a careful genitourinary history should be obtained prior to operation and a thorough examination should be made of the kidney before nephrectomy is done.

8. Liver: Hemorrhage from the liver was controlled in all cases by sutures, with or without free muscle graft, after devitalized fragments of hepatic tissue were removed. Under these conditions the danger

of bile peritonitis was thought to be avoided, and, indeed, no patients died from this cause.

9. Urinary Bladder: Perforations of the bladder were readily closed with Lembert or Cushing inversion sutures. Suprapubic cystostomy was not needed. A retention catheter was always inserted at the termination of the operation.

Postoperative Care.—In the immediate postoperative management of all patients with perforations, the gastrointestinal tract was kept completely at rest by allowing nothing by mouth and maintaining constant gastric suction with an indwelling catheter. Fluids were given parenterally to maintain nutrition and to replace losses. This involved the intravenous administration of dextrose, isotonic sodium chloride solution, protein hydrolysates, plasma, blood and vitamins as indicated. In planning the program of intravenous administration of fluids, an attempt was made to maintain a daily urinary output of about 1,200 cc. Gastric

TABLE 2.—*Postoperative Complications*

Evisceration	7
Separation of wound due to infection	5
Peritonitis with adynamic ileus	3
Uremia	3
Pneumonia	2
Septicemia	1
Thrombophlebitis	1

suction was terminated and oral feedings started as early during the postoperative period as possible, provided one or more of the following had occurred: (1) resumption of intestinal sounds, as shown by auscultation, and a decrease in abdominal distention; (2) repeated passage of gas or feces by rectum, and (3) retention of less than 50 per cent of a measured quantity of fluid given by mouth with the tube clamped off for two hours.

Chemotherapy.—Penicillin and sulfonamide compounds were used to a great extent in our series only in the last few years. Locally, sulfanilamide or succinylsulfathiazole were used in the peritoneum in one third of the cases. No particular ill effects were noted, but their efficacy was not proved.

POSTOPERATIVE COMPLICATIONS

The postoperative complications observed in the 95 cases are listed in table 2.

In the cases of evisceration, prompt abdominal closure was carried out with through and through retention sutures. Of the 7 patients involved, 2 died subsequently of generalized peritonitis and in 4 post-

operative ventral hernias developed. The 5 patients with separation of the wound due to infection were treated conservatively; secondary closure was done later. The fascia was intact in 3 of these patients, and ventral hernias did not develop in any.

MORTALITY

The mortality rate in this entire group of 134 cases was 12.7 per cent. However, since the deaths were limited only to patients operated on, the rate rises to 16.8 per cent. All deaths occurred only in the patients operated on in whom perforations were found; there were 66 in this group, which brings the mortality to 24.6 per cent of these patients. Of the 16 patients who died, only 7 entered the hospital in shock, and these were discussed separately in detail. The other 9 died some time after operation, 2 of delayed hemorrhage and shock, 2 of peritonitis, 2 of uremia, 2 of pneumonia and 1 of septicemia.

COMMENT

In a discussion of the treatment of penetrating abdominal wounds, many details might be emphasized. In this presentation, special attention was given to the group of patients entering the hospital in shock. Of the 95 patients operated on, 21 fall into this category. All had visceral lesions. It is interesting to note that 4 of them had no bleeding at operation, but merely perforations, and therefore might be classified as suffering from neurogenic shock. This observation serves to point out the fact that clinical shock in a patient does not necessarily mean that bleeding is present. All the patients in this group recovered. Ten patients suffered moderate to severe hemorrhage and recovered without adequate blood replacement. This is mentioned not in justification of insufficient transfusions but to show that when blood and plasma are not available other measures may be resorted to with some degree of success. The patients in this series were operated on promptly as a matter of policy; this permitted earlier control of the bleeding, which probably was just as important as adequate transfusions. Two patients died after operation, of peritonitis and uremia. Five patients who died might have been saved had an adequate amount of blood been available.

SUMMARY

Of 134 patients with penetrating abdominal wounds, 66 proved to have visceral injury; 21 of these entered the hospital in shock, 4 of whom showed no hemorrhage at operation and 10 of whom recovered without adequate blood replacement. Five deaths might have been avoided had larger quantities of blood been available. Thus, while patients in shock with penetrating wounds may recover without adequate

blood replacement, lives will be lost unless this method of therapy is available. There is no evidence from our cases that delay in operative treatment is justified.

CONCLUSIONS

Mortality may be reduced in cases of penetrating abdominal wounds by: (1) early diagnosis of penetration; (2) immediate administration of blood and plasma; (3) operation on patients in shock if there is no response to treatment within thirty minutes, and (4) the use of the antibiotics.

GASTRIC DIVERTICULA

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GASTRIC diverticula have been considered comparatively rare lesions.[1] Moses [2] reviewed the literature on this subject to 1946 and collected only 150 cases. Walters [3] reported on 5 patients in 1946 who were treated surgically, 4 by excision and 1 by inversion of the diverticulum, with relief of symptoms in all. Ferguson and Cameron [4] in 1947 successfully treated 2 patients by surgical inversion of the sac. Gerwig [5] described 2 cases of gastric diverticula in diaphragmatic herniations, in 1 of which resection was performed. Resnick [6] presented 3 cases, 1 previously reported and included in Moses' series, in which medical therapy seemed adequate. In 2 the diverticula were visualized gastroscopically without harm to the patient. Because of the paucity of case reports and the unusual surgical approach employed in the removal of the diverticula, 4 cases which were observed at Kennedy Hospital in the period from November 1946 to January 1948 are presented. This brings the number of reported cases to approximately 162.

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1. Rivers, A. B.; Stevens, G. A., and Kirklin, B. R.: Diverticula of the Stomach, Surg., Gynec. & Obst. **60**:106 (Jan.) 1935.

2. Moses, W. R.: Diverticulum of the Stomach, Arch. Surg. **52**:59-65 (Jan.) 1946.

3. Walters, W.: Diverticula of the Stomach, J. A. M. A. **131**:954 (July 20) 1946.

4. Ferguson, I. K., and Cameron, C. S.: Diverticula of the Stomach and Duodenum, Surg., Gynec. & Obst. **84**:292-300 (March) 1947.

5. Gerwig, W. H., Jr.: Diverticula and Other Mucosal-Lined and Pathologic Outpouchings of the Gastro-Intestinal Tract, Am. J. Surg. **74**:462-469 (Oct.) 1947.

6. Resnick, B.: Diverticulum of the Cardia of the Stomach, Am. J. Roentgenol. **55**:730-732 (June) 1946.

REPORT OF CASES

CASE 1.—J. M., a 37 year old white man, was admitted to the hospital on Feb. 11, 1948, with a history of midepigastric pain, nausea and vomiting every three to four months, lasting about a week, unaffected by alkali and aggravated by food. The patient had moderate insomnia and was a periodic drunkard. The attacks were not necessarily associated with consumption of alcohol. Physical examination revealed a normal-appearing white man. Studies of the blood, sedimentation rate and stools revealed nothing unusual. Gastric analysis revealed fasting achlorhydria, with a p_H of 1.4, one hour after stimulation with histamine.

Fig. 1 (case 1).—Lateral roentgenogram of abdomen after ingestion of barium meal showing diverticulum at posterior cardiac end of stomach.

A series of gastrointestinal roentgenograms demonstrated a diverticulum, 1.5 by 2.5 cm., arising on the posterior wall of the stomach adjacent to the lesser curvature near the cardia (fig. 1). Gastric mucosal folds could be followed through a narrow mouth into the diverticulum. The esophagus and duodenum were normal. On a bland diet with antacids, the patient became asymptomatic in two days, and he was discharged with instructions to return if diet alone failed to control his symptoms.

CASE 2.—W. S., a 23 year old white man, was admitted on Jan. 8, 1947, because of four days of diffuse epigastric pain, nausea and vomiting. This

symptomatology appeared in 1944, and recurred every two to three months. Physical examination revealed evidence of dehydration in an otherwise healthy, normal man. The results of a serologic test were negative. Studies of the blood and the sedimentation rate, gastric analysis and examination of the stools showed no abnormalities. A series of gastrointestinal roentgenograms demonstrated a diverticulum much like that seen in case 1. Drainage, however, could readily be accomplished in the left lateral decubitus position with the hips elevated. With the utilization of this maneuver, parenteral fluids, a convalescent ulcer diet and antacids, he became asymptomatic in five days. He was instructed in carrying out the diet and drainage and advised to return if his symptoms recurred. On April 13, 1948, he wrote to inform us that he had had recurrences which were controlled by diet and not severe enough to warrant hospitalization.

Case 3.—S. H., a 28 year old Negro, in 1943 experienced two or three isolated attacks of midepigastric pain, unrelated to food, each persisting for a period of one and one-half hours. Five months prior to his admission to the hospital on Nov. 14, 1946, epigastric pain recurred, and it continued daily until the time of his admission. The pain occurred usually before meals, late in the evening, and it had on occasion awakened him about four hours after he had fallen asleep. A series of gastrointestinal roentgenograms on Nov. 27 was suggestive of a diverticulum on the lesser curvature of the stomach 2.5 cm. from the cardia. No other abnormality was found (fig. 2*A*).

Gastroscopic examination on December 11 demonstrated an outpouching of the posterior wall of the stomach near the lesser curvature about 3 cm. from the cardia, which was estimated to be 1.5 cm. in length, with a perfectly round opening of about 0.5 cm. The mucosa of the outpouching was brown-red, in contrast to the orange-pink of the rest of the mucosa of the stomach. It exhibited no ulceration, but escaping from the pouch was a moderate amount of thick gray exudate. Because of a positive reaction to a serologic test the patient was given a course of penicillin and oxophenarsine hydrochloride. In spite of morning and evening drainage achieved in the right oblique Trendelenburg position and the administration of a bland diet and antacids between meals, there was only slight improvement in the patient's pain. In view of the persistent symptoms and no other demonstrable pathologic changes it was decided that resection of the diverticulum was in order.

On Feb. 11, 1947, under endotracheal anesthesia with the patient in the supine position and the left side elevated, the chest and abdomen were prepared with ether, alcohol and tincture of merthiolate® (sodium ethylmercurithiosalicylate) and draped. An incision was made over the lateral border of the left rectus muscle from a point 5 inches (12.7 cm.) below the costal margin, up to and across the costal margin and along the eighth interspace to the angle of the ribs. The rectus sheath and rectus muscle were divided lengthwise. The cartilage was divided between the eighth and ninth ribs. The serratus anterior and latissimus dorsi muscles were divided along the length of the incision. The posterior rectus sheath and the peritoneum were then opened and the incision continued intercostally to the angle of the ribs opening the pleural cavity. The diaphragm was then divided toward the esophagus for a distance of about 7 inches (12.7 cm.). Finochietto retractors were inserted between the ribs, which afforded excellent exposure of the area. The gastrohepatic ligament was then incised, and the diverticulum was found extending from the posterior wall of the cardiac end of the stomach about 1½ inches (3.8 cm.) below the entrance of the esophagus, with the apex of the diverticulum attached to the region of the tail of the pancreas and embedded in a group of enlarged lymph nodes. The diverticulum, with a

few of the nodes, was freed from the pancreas by sharp dissection (fig. 2*B*). Examination of the remainder of the stomach and duodenum revealed no evident pathologic changes. A narrow clamp was then placed across the diverticulum at its base, and it was excised with the knife. It was about 4 cm. long and 2 cm. wide at the base, tapering to about 0.5 cm. at the tip. The mucosal aspect of the tip appeared inflamed, but no actual ulcer was seen. The opening in the

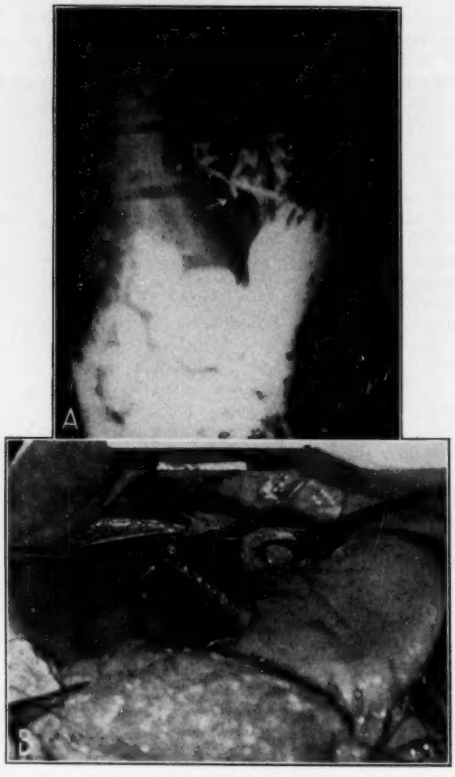

Fig. 2 (case 3).—*A*, lateral roentgenogram of abdomen after barium given by mouth showing outpouching at the gastric cardia posteriorly, which proved to be much larger at operation. *B*, photograph at time of operation showing the divided gastrohepatic ligament, the conical diverticulum, the divided diaphragm above it and the excellent exposure of the operative area.

stomach was closed with a continuous suture of intestinal chromic surgical gut for the first layer and interrupted 000 silk Cushing sutures for the seromuscular layer. The diaphragm was approximated with a row of 00 silk sutures through all layers, reenforced with a row of 000 silk sutures for the diaphragmatic pleura.

The costal cartilage was approximated with three no. 1 chromic surgical gut sutures through cartilage. The parietal pleura and the intercostal muscles were approximated with interrupted 00 silk sutures. A catheter was inserted into the pleural cavity through the posterior angle of the wound. The serratus anterior and latissimus dorsi muscles were approximated with interrupted 000 silk sutures. The peritoneum and the posterior sheath were closed with a continuous suture of 0 chromic surgical gut, the anterior sheath with interrupted 00 silk sutures and the subcutaneous tissue and skin with 0000 interrupted silk sutures. The lung was reexpanded by the anesthetist, and the catheter was withdrawn while suction was applied to it. A dry dressing was applied and the patient returned to his room in good condition.

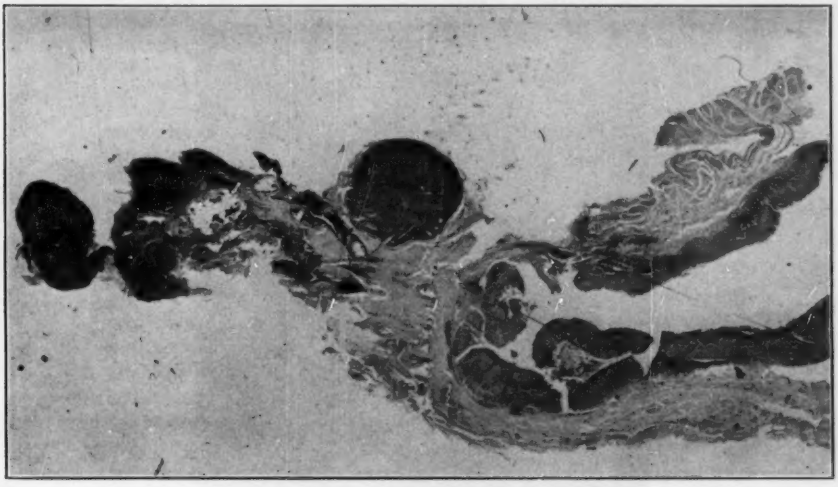

Fig. 3 (case 3).—Longitudinal histologic section of the excised diverticulum. Note lymph nodes and lymphoid tissue at apex.

During a one year follow-up no recurrence of the epigastric pain was noted, with only occasional tenderness at the site of the chondral incision. Pathologic examination of the resected specimen demonstrated a single conically shaped section of tissue measuring 3.5 by 2 cm. It was a pouchlike structure lined with gastric mucosa. Most of the wall of the structure contained submucosa and tunica muscularis. In one area layers of the wall were interrupted, and there was a considerable amount of hemorrhage at this point. Throughout the remainder of the section, the mucosa was intact. Small areas of recently extravasated blood were scattered irregularly through the mucosa and submucosa, and a minimal chronic inflammatory infiltration into some parts of the former was noted. On the distal end several collections of lymphoid tissue showing only localized reticuloendothelial hyperplasia were noted (fig. 3).

CASE 4.—R. S., a 37 year old white man, suffered a cerebral concussion resulting from a shell explosion in 1943. After this he had recurrent episodes of

burning pains in the left subcostal margin, controlled by bland diet and aggravated by spicy or greasy foods. Prompt relief from pain could usually be secured by the ingestion of antacids. His first admission to the hospital occurred in October 1947. Relief from pain was obtained after a bland diet, antacids and morning and evening drainage were given. He returned in January 1948 because of a recurrence of symptoms and a single episode of nausea and vomiting. Examination revealed only epigastric tenderness on deep palpation. Blood studies, serologic tests, determination of the sedimentation rate and examination of the stools showed nothing remarkable. Gastric analysis revealed a hypersecretory response to histamine. A series of gastrointestinal roentgenograms demonstrated a diverticulum similar to that in case 1.

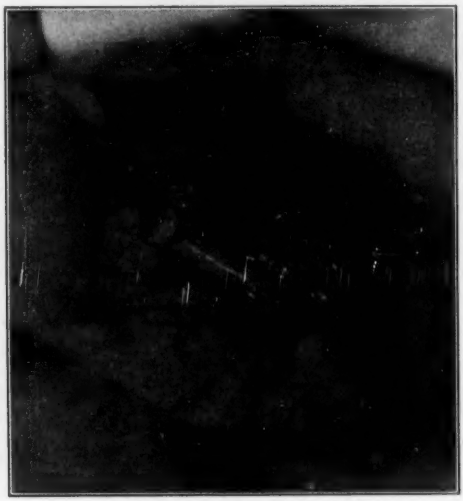

Fig. 4 (case 4).—Photograph showing spherical diverticulum still attached to stomach.

Because of recurrence of symptoms in spite of good medical management and the absence of other gastrointestinal changes, resection of the diverticulum was elected.

On Jan. 16, 1948, under endotracheal anesthesia and with the patient in the supine position and the left side slightly elevated, the chest and abdomen were prepared with ether, alcohol and sodium ethylmercurithiosalicylate and draped. A transverse incision was made across the left upper quadrant dividing the rectus muscle, sheath and peritoneum. The incision was continued laterally along the eighth interspace, opening the chest as in the previous case. The left triangular ligament of the liver was divided and the left lobe of the liver retracted with a stockinet-covered Deaver retractor. The spleen, which was prominent in the field, was retracted laterally. The gastrolienal ligament was divided for about 5 inches (12.7 cm.) along the fundus, which permitted downward medial

displacement of the fundus, but the diverticulum was not located. Division of the gastrohepatic ligament and left gastric artery similarly resulted in failure to locate the lesion. Thereupon, the stomach was opened anteriorly, below the esophagus, for a distance of about 6 cm. and the interior explored. The pylorus appeared normal. The esophageal opening showed no pathologic process. The entire gastric mucosa presented a normal appearance. About 4 cm. below the esophagus, posteriorly, there was an opening which allowed the entrance of the index finger into a pouch about 2 cm. in diameter. On inspection of this on the outer aspect of the stomach, it was seen to be attached to the posteromedial edge of the spleen. The tip was separated from the spleen and the gastrotomy wound closed with a continuous suture of intestinal 00 chromic surgical gut for the inner layer and interrupted Lembert 000 silk sutures for the seromuscular layer. Before resection of the diverticulum, a photograph was taken (fig. 4). The lesion was resected and the base closed as in the previous case. Inspection of the specimen revealed some scarring of the mucosa at the apex of the diverticulum. Closure of the wound was performed as in case 3.

Unfortunately, in transport from the photographic to the pathology laboratory the specimen was lost, so that histologic sections were not secured. The patient's postoperative course was uneventful. Two months after discharge, he informed us that there was no question that he was benefited by the operation. Large meals, however, produce a sensation of distention and of mild pain in the back below the left costal margin.

COMMENT

Relief was secured on a medical regimen alone in case 1, in case 2 only partial relief was obtained, and in cases 3 and 4 surgical intervention was resorted to when medical management did not result in satisfactory amelioration of symptoms. It is evident that the mere establishment of a diagnosis of gastric diverticulum does not prove a causal relationship. The diagnostic acumen of the physician will be put to the test in each case. It seems reasonable to utilize the medical therapy of bland diet, postural drainage and antacids first, accompanied with the psychotherapy of reassurance before resorting to surgical treatment.

The gastric diverticula described in this paper were discovered during routine roentgenologic examination of the gastrointestinal tract. Careful observation of the cardia during the entry of the first amounts of barium swallowed, demonstration of the mucosal pattern by manual displacement, examination in recumbent and Trendelenburg positions in varying oblique projections, and reelevation of the patient to the vertical position, all with minimum barium filling, are the essential steps in the successful demonstration of gastric diverticula. A common experience of all those adept at roentgenologic examination of the gastrointestinal tract, but perhaps not sufficiently emphasized in the literature, is the fact that diverticula and ulcer craters will often reveal themselves readily during the undisturbed advance of the first bolus of barium through the fundus and pars media of the stomach, only to empty themselves and become invisible within the span of a few seconds.

Their successful demonstration thereafter is often only possible by carefully directed efforts centered on the region of initial suspicion. If an outpouching is thus discovered, diverticulum, benign ulcer crater, ulceration in neoplasm and contour variations within the limits of normal deserve consideration in the differential diagnosis. The gastric diverticulum is found in the immediate vicinity of the cardia on the posterior wall of the stomach, close to the lesser curvature, where benign ulcers are extremely rare. While diverticula in other portions of the stomach have occasionally been mentioned, they constitute a finding of extreme rarity. The diverticulum is usually spherical, with a distinct neck giving it a flask-shaped appearance. Its contours are regular, mucosal folds extend into the neck and the gastric wall in its immediate vicinity does not deviate from the normal. The gastric ulcer is usually less deep and does not have a distinct neck, mucosal folds do not enter the crater and the outpouching is not pedunculated and therefore cannot be displaced by change in position or pressure in relationship to the adjacent gastric wall. Contour irregularity, infiltration of the adjacent gastric wall with marginal overhang and disturbance of the adjacent mucosal structure tend to indicate the presence of neoplastic change. Deviation from the classic appearance of the diverticulum will be found in the presence of secondary inflammatory changes within it. These may produce irregularity of contour, absence of demonstrable mucosal pattern, secondary smaller outpouchings in the perimeter of the diverticulum and such unusual shapes as narrow elongated appendix-like protrusions, sometimes adherent to adjacent structures and not evacuable by gravity. Our case 3 is an illustration of such findings. An independent roentgenologic diagnosis at the first examination might be impossible in such circumstances. In addition to gastroscopy, repeated roentgen examination demonstrating the absence of either progressive or retrogressive changes might furnish supporting evidence.

Definite evidence of inflammation was obtained by histologic examination in case 3. In case 4 the mucosal scarring in the apex of the excised specimen was in favor of previous ulceration. In addition to ulceration and inflammation, hemorrhage, neoplasm, perforation and pancreatic tissue in the tips of diverticula have been reported.[7]

Since the gastric diverticulum is so commonly located on the posterior surface of the cardiac end of the stomach, exposure of the lesion for resection presents a difficult problem. In the majority of reported cases in which surgical treatment was given the abdominal route alone

7. (*a*) Tilford, D.: Diverticula of the Stomach, Canad. M. A. J. **50**:526-529 (June) 1944. (*b*) Tracey, M. L.: Gastric Diverticula, Gastroenterology **1**:518-531 (May) 1943. (*c*) Brown, P. W., and Priestley, J. T.: Massive and Recurrent Gastrointestinal Hemorrhage from Diverticulum of the Stomach, Staff Meet., Mayo Clin. **13**:270 (April 27) 1938.

was employed.[8] In at least four instances the lesion was not found by that approach,[9] and in one of these it was located and resected at a second abdominal exploration.[3] In several articles on the subject from good clinics, the difficulty of resection of these lesions due to inaccessibility is described.[10] Excision, rather than inversion of the diverticulum, has been practiced by most surgeons dealing with this lesion.[11] This would seem the more desirable policy in good hands, in view of the possible presence of pancreatic tissue, ulcer or neoplasm in the tip.[7]

The combined thoracoabdominal approach is finding increased popularity for resection of malignant lesions of the lower part of the esophagus and the gastric cardia[12] and for splenectomy.[13] Likewise, exposure of gastric diverticula at the cardiac end of the stomach and their excision are best accomplished by way of the thoracoabdominal approach because of the following reasons: The exposure is more complete. There is less danger of hemorrhage since the left gastric and short gastric vessels can be divided under direct vision. There is less shock. A lighter plane of anesthesia and less of the anesthetic agent are required. The postoperative condition is better than when the abdominal route is used.

To approach the diverticulum in the region of the gastric cardia the abdominal incision, longitudinal or transverse, is extended intercostally along the left eighth interspace, the pulmonary ligament is divided and the diaphragm is split down to the esophageal hiatus. The rib spreaders are then inserted, opening the operative site like a book. By division

8. (*a*) Love, McN.: Gastric Diverticulum, Brit. J. Surg. **30**:180-181 (Oct.) 1942. (*b*) Martin, L.: Diverticula of the Stomach, Ann. Int. Med. **10**:447 (Oct.) 1936. (*c*) Shiftlett, E. L.: Diverticula of the Stomach, Am. J. Roentgenol. **38**:280 (Aug.) 1937. (*d*) Moses.[2] Walters.[3] Tilford.[7a] Tracey.[7b] Brown and Priestley.[7c]

9. Walters.[3] Martin.[8b] Shiftlett.[8c]

10. (*a*) Jordan, S. M., and Lahey, F. H.: Diverticula of the Alimentary Tract, S. Clin. North America **6**:747, 1926. (*b*) Tracey, M. L.: Gastric Diverticula, Lahey Clin. Bull. **3**:182-187 (Oct.) 1943. (*c*) Paulson, D. L.: Transthoracic Gastric Surgery with Report of a Transthoracic Resection of a Diverticulum of the Stomach, J. Thoracic Surg. **13**:518-522 (Dec.) 1944.

11. Moses.[2] Walters.[3] Love.[8a] Tracey.[7b] Brown and Priestley.[7c] Martin.[8b] Paulson.[10c]

12. Garlock, J. H.: Combined Abdominothoracic Approach for Carcinoma of the Cardia and Lower Esophagus, Surg., Gynec. & Obst. **83**:737-741 (Dec.) 1946. Harper, F. R.: Thoracoabdominal Approach to the Upper Abdomen, ibid. **84**: 331-332 (March) 1947. Humphreys, G. H., II: An Approach to Resection of the Esophagus and Gastric Cardia, Ann. Surg. **124**:288-300 (Aug.) 1946.

13. Carter, B. N.: The Combined Thoracoabdominal Approach with Particular Reference to its Employment in Splenectomy, Surg., Gynec. & Obst. **84**:1019-1028 (June) 1947.

of the gastrolienal and gastrocolic ligaments and the drawing of the fundus down medially, the diverticulum is exposed. For diverticula nearer the lesser curvature, the proximal end of the gastrohepatic ligament may be divided along with the left gastric artery, if necessary, to expose the lesion. If the diverticulum is not located with these maneuvers, it is suggested that a small incision into the stomach be made anteriorly, the opening into the diverticulum in the posterior wall located and a finger or blunt instrument inserted into it, outlining it on the outside wall of the stomach, as in case 4. The stomach is closed and the diverticulum resected at its base. The tip of the diverticulum will usually require freeing from surrounding structures. In 1 of our patients operated on it was adherent to the tail of the pancreas and in the other it adhered to the upper medial aspect of the spleen.

SUMMARY

Four cases of gastric diverticula are reported.

Two cases were successfully controlled by medical measures, which are not too demanding or disagreeable. Surgical intervention should be employed only if medical measures fail to control the patients comfortably.

Successful resections of the two medically uncontrolled diverticula were accomplished by means of the thoracoabdominal incision. The advantages of this approach are discussed.

EVALUATION OF GASTROSTOMY FOR MALIGNANT DISEASE

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EARLY HISTORY OF GASTROSTOMY

PRESUMABLY the first gastrostomies were the accidental results of trauma and were mere curiosities, but their occurrence suggested the possibility of intentional creation of such artificial fistulas for the relief of esophageal obstruction. Sédillot [1] is generally conceded to have been the first surgeon to perform gastrostomy, but his patients, operated on in 1849 and 1853, failed to survive the immediate postoperative period. To Sydney Jones,[2] a London surgeon, must go the credit for having first successfully created an artificial gastric fistula since his patient, operated on in 1875, survived for forty days after the operation.

The first attempt at gastrostomy in the United States was made in 1870 by Maury.[3] His patient survived only fourteen hours. In 1879 Staton [4] in North Carolina operated on a child near starvation consequent on stricture of the esophagus due to the ingestion of lye, and the child was in good health six months later. After this beginning many such operations were apparently performed, since Samuel Gross [5] in 1883 was able to collect a series of 137 patients who had undergone gastrostomy. There were 31 operative deaths, 64 deaths in the first postoperative month, and 42 survivors for longer periods.

It is easy to see how surgeons of that and subsequent periods, confronted by patients with esophageal obstruction from whatever cause, and lacking more physiologic surgical procedures, welcomed an opera-

From the Department of Surgery of the Johns Hopkins School of Medicine and the Johns Hopkins Hospital.

1. Sédillot, C. E.: Opération de gastrostomie, pratiquée pour la première fois le 13 novembre 1849, Gas. méd. de Strasbourg **9**:366, 1849.

2. Jones, S.: Gastrostomy for Stricture (Cancerous?) of the Oesophagus: Death from Bronchitis Forty Days After Operation, Lancet **1**:678, 1875.

3. Maury, F. F.: A Case of Stricture of the Oesophagus in Which Gastrostomy Was Performed, Am. J. M. Sc. **59**:365, 1870.

4. Staton, L. L.: Gastrotomy or Gastrostomy, North Carolina M. J. **6**:183, 1880.

5. Gross, S. W.: A Case of Gastrostomy for Carcinoma of the Oesophagus, with a Brief Analysis of the Results of One Hundred and Thirty-Seven Cases of a Similar Nature, M. News **43**:591, 1883.

tion which, if successful, despite the inherent disadvantages of life with a gastric fistula, seemed to postpone death. Perhaps many patients also welcomed the operation. But with our present methods of successful esophagectomy, antethoracic esophagoplasty and esophagogastrostomy, only those patients with tumors which are inoperable because of extension or metastasis or patients considered unlikely to survive extensive surgical procedures are treated by palliative gastrostomy. The benefits of gastrostomy in such patients are dubious and may even be outweighed by the unpleasant results. It is for this reason that a review of the results of gastrostomy for malignant disease over a twenty-one year period at the Johns Hopkins Hospital was undertaken.

CASES IN THE JOHNS HOPKINS HOSPITAL

Between September 1925 and August 1946, 142 patients in the Johns Hopkins Hospital were subjected to gastrostomy for dysphagia thought at the time of discharge from the hospital to have been due to malignant disease. Subsequent examination of the records shows that for 4 of these patients the diagnosis was erroneous. One patient had an extrinsic mediastinal mass pressing on but not invading the esophagus. One had a clearly demonstrated aortic aneurysm producing dysphagia. Another patient, for whom a pathologic diagnosis of inflammation was made after examination of tissue removed from the esophagus, is now, three years later, gaining weight and in good health. In the fourth patient a large gastric filling defect was seen on roentgenologic examination, and during laparotomy she was thought to have extensive carcinoma, but all symptoms disappeared and the gastrostomy opening was permitted to close after antisyphilitic treatment, therapeutic proof that the patient had gastric syphilis, since she is now well five years after operation.

Examination of tissue removed from the lesion was made by a pathologist in only 88 of the remaining 138 cases, in 70 at biopsy and in 18 at autopsy. Eighty of these specimens showed malignant disease; eight of the biopsies failed to reveal neoplasm.

It will be seen from table 1 that more than three fourths of the gastrostomies were performed for lesions of the esophagus or stomach and most of the remaining gastrostomies were performed for carcinoma of the pharynx, larynx and tongue. There were a few other types of malignant disease for which gastrostomy was done. In 54 of these patients, or 39 per cent, distant metastasis or extension to other organs was recognized either before or after death; in the remaining 84, or 61 per cent, neither was thought to be present. The survival range and average time were essentially the same in both groups.

Of the 138 patients in whom gastrostomy was performed for malignant disease, 10 were subjected to some other procedure either simul-

taneously or subsequently. This was usually esophageal resection, and as an attempt was often made to bridge the defect by some means, the success or failure of the operation in these patients cannot be attributed to gastrostomy. Furthermore, there were 25 patients, mostly operated on in the early years of the period under discussion, about whom no follow-up information could be obtained. Omission of these leaves 103 patients who underwent gastrostomy alone for malignant disease and who could be followed. All are dead, 29 having died in the hospital during the postoperative period and 74 having been discharged from the hospital to survive for varying lengths of time. During the

TABLE 1.—*Organs Involved*

Organ	No. of Cases	%
Esophagus	69	50
Stomach	37	27
Epiglottis and larynx	17	12
Tonsil and pharynx	4	3
Tongue	4	3
Thyroid	2	2
Lungs and bronchi	2	2
Cervical nodes (Hodgkin's disease)	1	0.5
Mediastinal nodes (metastasis from carcinoma of breast)	1	0.5
Sarcoma in mediastinum	1	0.5
	138	

TABLE 2.—*Cause of Death in the Hospital*

Underlying malignant process or no assigned cause	15
Pulmonary complications (excluding extension of tumor into lung, including pneumonia, pulmonary embolism)	12
Surgical accident (tube in peritoneum)	1
Miscellaneous (arterial embolus)	1
	29

period under consideration 38 patients underwent gastrostomy for benign conditions; 8 of them died in the hospital from two to sixty-five days after operation, a mortality rate of 18.4 per cent. Five of the patients died of pneumonia or pulmonary abscess, 2 of pulmonary embolism and 1 of peritonitis. The operation itself, then, is not without hazard in the dysphagic patient, whatever the underlying lesion may be.

Table 2 shows that of the 29 patients who died in the hospital 15 died of no assigned cause other than the underlying condition. Twelve patients died of pulmonary complications, including embolism and pneumonia but not including extension of the neoplasm into the lung. One patient died of peritonitis after a gastrostomy tube which was being replaced passed out of the tract and into the peritoneal

cavity. Another patient, already cachectic, had a large femoral arterial embolus and died after embolectomy.

Table 3 gives the longest and the shortest survival periods in postoperative days for the patients grouped according to the location of the tumor. Obviously the average survival time is not statistically significant in any group since no group is of great size. It is of interest, however, that the average survival time as well as the range is essentially the same for all groups containing even as many as 4 cases. The longest survival period was that of a man who lived nearly two years after gastrostomy for microscopically proved carcinoma of the epiglottis, which required tracheotomy six weeks after gastrostomy. One

TABLE 3.—*Survival Range and Average in Days*

Location	No. of Cases Followed	Longest	Shortest	Average
Stomach	25	517	3	140
Esophagus	51	713	1	125
Epiglottis and larynx	14	726	0	130
Tonsil and pharynx	2	132	10	71
Thyroid	2	89	15	52
Tongue	4	263	39	132
Lungs and bronchi	2	13	3	8
Other locations	3	76	26	43
Entire group	103	726	0	123

TABLE 4.—*Survival Range and Average in Days**

Location	No. of Cases Followed	Longest	Shortest	Average
Stomach	21	404	3	101
Esophagus	49	713	1	106
Tongue	3	130	39	88
Entire group	96	726	0	103

* Patients for whom the diagnosis was doubtful were omitted.

may wonder at the value of two years of life for a person who has undergone gastrostomy and tracheotomy and for whom the outlook is hopeless.

Twenty-one patients lived over six months after gastrostomy, and a review of their histories leaves the diagnosis of carcinoma questionable in 7 cases. In 4 of these 7 patients the diagnosis of gastric carcinoma was made during laparotomy without performance of a biopsy, and they survived 210, 300, 347 and 517 days respectively. One of these patients had 22 units of free gastric acidity. All had a negative reaction to the serologic test for syphilis. The fifth patient, who survived for 703 days after gastrostomy for what was diagnosed as gastric carcinoma on roentgenologic evidence alone, had had a condition diagnosed as pylorospasm on roentgen examination two years previously.

The sixth patient, who survived gastrostomy for 495 days, had a low esophageal obstruction of smooth outline, said by both roentgenologist and esophagoscopist not to be carcinoma. In the seventh patient, who was known to have tuberculosis with pleural effusion and a testicular gumma, biopsy of the lingual lesion was not conclusive for carcinoma. He survived gastrostomy for 263 days.

It is interesting to omit these 7 patients from the series and to note the result on the survival period as indicated in table 4. The survival range is not affected except in the individual groups, but the average survival time falls nineteen days in the group with gastric carcinoma and thirty-nine days in the group with esophageal carcinoma.

At best, these figures indicate that the rare patient with dysphagia on a malignant basis may hope for up to seventeen months of life after gastrostomy if the lesion is gastric and possibly six months longer if it is esophageal or laryngeal but that the general run of patients will be dead in less than four months in either group. Whether so short a reprieve from inevitable death outweighs the inherent unpleasantness, leakage and odor resulting from gastrostomy and the possible resultant ostracism is at least highly questionable. An eloquent commentary on this problem is the fact that 2 patients in this series, after trying to adjust themselves to a gastrostomy, voluntarily starved to death.

COMMENT

Recent writers on gastrostomy have divergent views on its advisability. Thorek [5a] unequivocally advised the performance of gastrostomy for any lesion which interferes with deglutition and which cannot be extirpated. He even advised jejunostomy when involvement of the stomach is so extensive as to preclude gastrostomy. Adams [6] recommended gastrostomy for any esophageal obstruction, either as a preliminary to resection or as a definitive palliative procedure. On the other hand, when Meyer and Kozoll [7] studied 80 patients who had been subjected to gastrostomy for carcinoma of the esophagus at the Cook County Hospital between 1941 and 1944, they found that 43 died in sixty days—2 on the first postoperative day, 19 in the first week, 18 more in the first month and 4 in the second month. They concluded that the results of gastrostomy were so wretched as to make it a futile procedure and urged esophageal resection and some type of anastomosis in every case, whatever the mortality might be.

5a. Thorek, M.: Gastrostomy; The History of Its Development, Indications and Contraindications, Rev. Gastroenterol. **12**:347, 1945.

6. Adams, H. D.: Gastrostomy, S. Clin. North America **21**:763, 1941.

7. Meyer, K. A., and Kozoll, D. D.: Gastrostomy, editorial, Surg., Gynec. & Obst. **81**:221, 1945.

A recent review by Cooper and Buxton [8] of patients subjected to gastrostomy over a twelve year period at the University Hospital, Ann Arbor, Mich., included 134 patients in whom the operation was performed because of an inoperable neoplasm. Of these patients, 79 were dead in three months, only 18 were alive six months after operation and only 3 survived the first postoperative year. These authors concluded that "no significant extension of life was gained for these patients" and cast grave doubt on the advisability of gastrostomy for inoperable neoplasm.

At the time when many of the patients in our series were operated on, gastrostomy was the only procedure performed for esophageal carcinoma; the series, therefore, included patients with early lesions who would now be subjected to esophageal resection. This consideration would tend to make the periods of survival longer in our series than might be currently expected among those persons now condemned to gastrostomy. Thus the outlook for gastrostomy at this time is bleak indeed.

The most cogent objection to abandoning the inhumane operation of gastrostomy for dysphagia due to malignant neoplasms is social and ethical. Most patients with such lesions enter hospitals where beds can ill be spared for those awaiting death from cancer, and it is considered proper to send such patients home after construction of a gastric fistula. It is a debatable point whether it is greater torture for a family to observe the progress of malignant cachexia over a four month period of gastrostomy life or to watch the rapid decline of a patient with obstruction burdened by neither gastrostomy nor parenteral feedings. It would seem that, at least in some cases, with adequate medication, the latter course is preferable for patient and family.

SUMMARY

In the treatment of patients with dysphagia due to malignant neoplasms, each instance must be individually considered. If resection is remotely possible, the tumor should be extirpated. In many patients, because of their debility or the extent of the tumor, the lesion cannot possibly be resected. In view of the mortality attendant on gastrostomy in such patients, the brief postponement of death and the unpleasantness of life with a gastric fistula plus esophageal or pharyngeal obstruction, it may be kindest and wisest to withhold operation, provided there is unequivocal histologic evidence of the malignant nature of the obstruction.

8. Cooper, D. R., and Buxton, R. W.: Gastrostomy, Surgery **23**:821, 1948.

TUMOR OF THE CAROTID BODY ASSOCIATED WITH NODULAR GOITER

Report of a Case

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THE SMALL encapsulated structure at or near the bifurcation of the common carotid artery and known as the carotid body has received sporadic attention since its first description by von Haller in 1743. The physiology of this organ has received most of the attention, although its pathologic lesions have not been exempt from discussion. Opinions still differ as to the origin of the carotid body even though the majority now consider it similar to that of the adrenal medulla.

In 1944 a concise summary and review of the physiology of the carotid body was presented by Dripps and Comroe.[1] Briefly, it may be said that this body is a chemoreceptor, in contrast to the carotid sinus, which is a pressoreceptor. Response to stimulation of the former results in increased respiratory rate, increased sympathetic activity and increased cerebral cortical activity.

Atrophy and fibrosis may be found in elderly subjects, but the principle pathologic lesion noted in this organ is a tumor. Such tumors are not common, since there are less than 300 reported in the literature, with a frequency about equally divided between males and females. They may occur at any age but are more common in the fourth and fifth decades. Although bilateral involvement has been noted, tumors of the carotid body are usually unilateral, with no preference for either side. The size varies, with an average of 3 to 4 cm. in diameter. The gross appearance of these tumors is generally that of an encapsulated, lobulated, mass, usually brown or grayish brown. They adhere to and often encircle the great vessels.

From the Department of Surgery, Albany Medical College.

1. Dripps, R. D., Jr., and Comroe, J. H., Jr.: Clinical Significance of Carotid and Aortic Bodies, Am. J. M. Sc. **208**:681-694 (Nov.) 1944.

Microscopically, small cells predominate in a uniform pattern. Harrington [2] classified the tumors in two groups on an architectural basis: (1) alveolar or insular; (2) peritheliomatous. The former present well defined alveolar-like groups of polyhedral cells with small fibrous bands. The latter present a less orderly arrangement, although some effort toward alveolar formation may be seen, with small clumps of cells separated by highly vascular connective tissue. Hyalinization of the connective tissue is often a prominent feature. Some cells display eosinophilic cytoplasm and numerous vacuoles with one or more hyperchromatic nuclei. All the tumors are considered potentially malignant. Actual malignancy is demonstrated by cellular variation, invasion of the capsule and mitosis. Willis,[3] however, said: "With few and doubtful exceptions, tumors of the carotid body are benign, growing slowly, remaining sharply circumscribed and producing no metastases."

Few, if any, symptoms are caused by these tumors. Usually they present as a painless nodule in the upper part of the anterior cervical triangle. The patient complains of a painless lump of several years' duration jutting out from under the anterior margin of the sternocleidomastoid muscle. Although firm, such a tumor may be compressible because of vascularity. Because they arise in relation to the carotid bifurcation, carotid body tumors are deep seated and are never attached to the skin. They usually present some lateral mobility but little or none in the vertical direction because of their attachments. They progress gradually in size, and the only symptoms as a rule are the result of pressure on the neighboring structures, e.g., sympathetic, vagus, hypoglossal or recurrent laryngeal nerves, pharynx and esophagus.

Preoperative diagnosis of these tumors is often difficult. Suspicion should be stimulated by any mass in the superior aspect of the anterior cervical triangle. In the differential diagnosis consideration should be given to branchial cleft cyst, tuberculous adenitis, aberrant thyroid, aneurysm and tumors of nerve structures. The importance of carefully considering the diagnosis is apparent, since surgical removal of these tumors is the treatment of choice and because their intimacy with the great vessels in the neck and with the major nerves in this area make damage to, or sacrifice of, such important structures a potent possibility. Accordingly, there should be proper preoperative evaluation of the patient regarding the adequacy of collateral circulation in the event that the carotid artery should require ligation.

2. Harrington, S. W.; Claggett, O. T., and Dockerty, M. B.: Tumors of Carotid Body: Clinical and Pathologic Considerations of Twenty Tumors Affecting Nineteen Patients (One Bilateral), Ann. Surg. **114**:820-833 (Nov.) 1941.

3. Willis, R. A.: Pathology of Tumours, St. Louis, C. V. Mosby Company, 1948, p. 875.

Phelps and others [4] found that nearly all the operative deaths were in cases that required ligation of the carotid vessels. The carotid vessels had been ligated in the patients who died in Harrington's series. Harrington further stated that in approximately one half of the cases of carotid body tumor it is necessary to ligate the carotid vessels, a procedure that is associated with a 30 per cent mortality. Preoperatively, external compression of the common carotid artery as described by Matas [5] is of value, for, as Dandy [6] has pointed out, ligation of the common carotid artery is contraindicated when the Matas test cannot be successfully carried out. Some authors, including Harrington and his group, have suggested repeated external compression of the common carotid artery at frequent intervals daily, to encourage collateral circulation. Dandy has stated that partial closure of the common carotid artery quickly encourages collateral circulation and ligation can be accomplished safely at the later date in patients who would otherwise not tolerate it.

PRESENTATION OF A CASE

G. H., a 62 year old white man, had the chief complaint of "two masses in the neck." One mass was at the angle of the jaw on the right side. This had been present for ten to twelve years. It had long been a small asymptomatic nodule that caused the patient no concern. A few months before his admission to the hospital it showed slow but steady growth and became somewhat painful to touch. The second mass had gradually appeared during eight months at the base of the neck on the left, anteriorly. There was no evidence of hyperthyroidism. There were no pressure symptoms from either tumor. There was no history of weight loss and no history of cardiorespiratory disturbance. For one month prior to his admission the patient had been taking strong iodine solution, and during that time he noted a definite decrease in the size of the tumor mass at the base of the neck anteriorly.

The past history and the family history were irrelevant.

Physical examination revealed a well developed and well nourished white man in no acute distress, appearing about the stated age. The blood pressure was 205 systolic and 114 diastolic, the pulse rate 88 and the temperature normal. A firm mass was noted in the right side of the neck presenting from beneath the anterior margin of the sternocleidomastoid muscle at the angle of the mandible. It was deeply fixed, with only slight lateral mobility. In the base of the neck, slightly to the left of the midline, there was a somewhat softer tumor, not fixed to surrounding structures, which rose when the patient swallowed. The heart, lungs and abdomen revealed no pathologic changes.

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4. Phelps, F. W.; Case, S. W., and Snyder, G. A. C.: Primary Tumors of Carotid Body, West. J. Surg. **45**:42-46 (Jan.) 1937.

5. Matas, R.: Testing the Efficiency of the Collateral Circulation as a Preliminary to the Occlusion of the Great Surgical Arteries, J. A. M. A. **63**:1441-1447 (Oct. 24) 1914.

6. Dandy, W. E.: Results Following Ligation of the Internal Carotid Artery, Arch. Surg. **45**:521-533 (Oct.) 1942.

Laboratory Data.—Urinalysis and routine blood counts gave results which were within normal limits. A roentgenogram of the chest revealed a mass in the neck extending down retrosternally, with some displacement of the trachea to the right.

On Dec. 3, 1946, under general anesthesia, a low collar incision was made and the pretracheal muscles were divided in the midline. The left lobe of the thyroid gland was found to be the site of multiple cystadenomas, with evidence of old hemorrhage in some. The substernal extension was delivered easily. A subtotal resection was carried out and the capsule closed. The wound was closed in layers.

An oblique incision was then made over the mass under the angle of the right jaw. When the sternocleidomastoid muscle was retraced laterally, the tumor presented as a firm, nodular mass about the size of a plum at the bifurcation of the common carotid artery. The mass was yellowish white. The tumor was carefully dissected from the major vessels and nerves; the internal jugular vein was injured and had to be ligated. The wound was closed in layers. The postoperative course was uneventful.

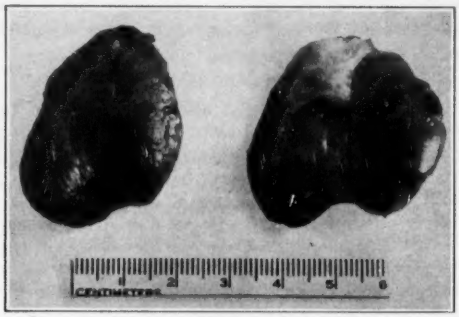

Fig. 1.—External surface of tumor of the carotid body grooved by carotid artery bifurcation and cut surface of same tumor.

Dr. A. W. Wright, head of the department of pathology, gave the following report on the tumor of the carotid body.

Gross Description.—The specimen is a heart-shaped (fig. 1), well encapsulated tumor mass of rubbery consistency. It measures 4 by 3.5 by 2 cm., is somewhat lobulate and has a rather deep groove cutting across the broadest surface, where there appears to have been pressure produced by some adjacent structure, presumably an artery. The cut surfaces of the growth are smooth, tan in color and focally hemorrhagic and are divided into the irregular lobules by fibrous septums.

Microscopic Description.—Sections from the mass show it to be a tumor composed of cells which resemble those of the carotid body (fig. 2). The entire mass is surrounded by a fairly thick fibrous capsule, which in places seems to be infiltrated by tumor cells. From the capsule irregular fibrous strands extend inward, dividing the neoplasm into lobules. The neoplastic cells are large and epithelioid, contain abundant pale-staining cytoplasm and are indefinitely outlined. The striking histologic feature is their arrangement in alveolar masses within the lobules. The cells in the alveolar masses vary in number, though in general the number is small. Sometimes the cell accumulations are large and loose, but more often they are small and rather compact. In no case is there evidence of

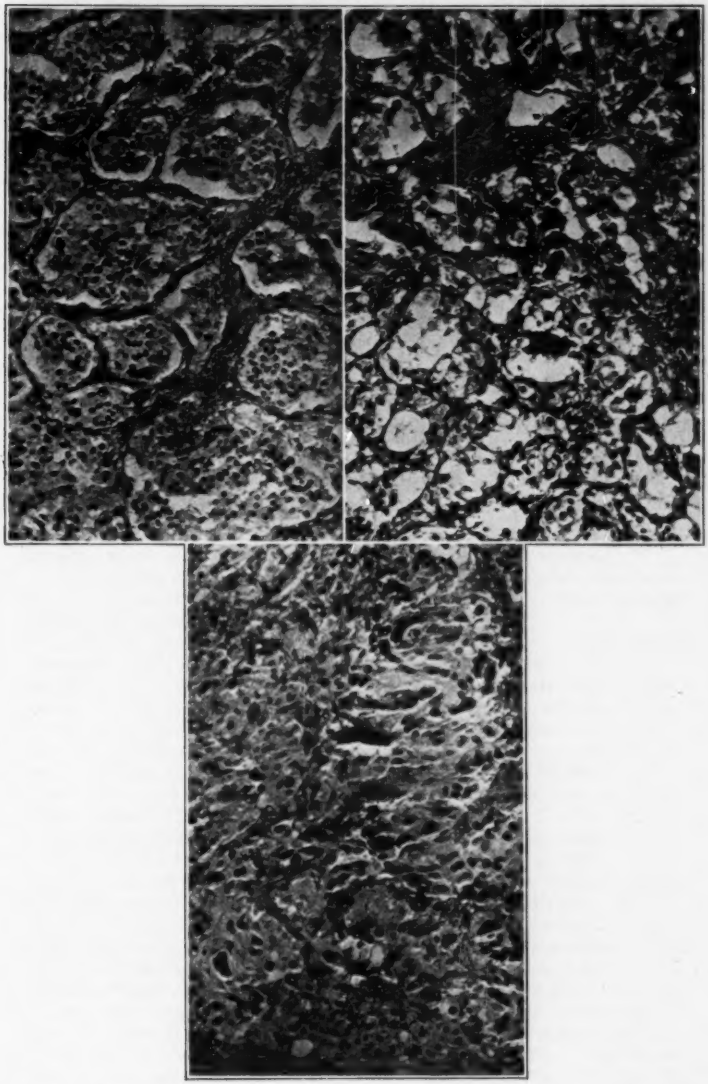

Fig. 2.—Variation in arrangement of the tumor cells in a tumor of the carotid body.

lumen formation, though sometimes the alveolar masses contain irregular vacuole-like spaces which unquestionably result from the degenerative changes in some of the cells. Cytoplasm, as previously noted, is abundant, and nuclei are usually single, small, round or oval, with abundant chromatin. Many of them stain lightly because of the fineness of the chromatin granules, but some of them are large, lobulated and hyperchromatic. Multinucleate cells are common. Mitoses are not found. In many situations the cells making up the alveolar masses show degenerative changes in the form of cytoplasmic granules, hyaline droplets or large vacuoles, which result in distortion of the shape of the cells and not infrequently lead to the formation of the irregular spaces described. While the alveolar groups tend to be clearly demarcated from each other, this demarcation is due chiefly to the presence of flat, compressed endothelium-like cells which, together with delicate, fibrous bands, form the stroma of the tumor. Blood vessels are numerous, and minute hemorrhages are occasionally seen. The neoplasm is a typical perithelioma of carotid body origin or so-called carotid body tumor.

COMMENT

The finding of a tumor of the carotid body is rare, and the association of such a tumor with a nontoxic nodular goiter is unusual. Although malignant tumors of the carotid body are described we believe that the tumor in the case here reported represents a benign lesion. The patient has been followed at regular intervals, and twenty-one months postoperatively he is still living, free from symptoms or recurrence.

BEHAVIOR OF GELATIN FILM IN HUMAN TISSUE AND AS AN AID IN THE REPAIR OF PLEURAL DEFECTS

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THE CLINICAL use of absorbable gelatin materials has been accepted as a valuable surgical adjunct in the past few years.[1] Our interest in the surgical use of gelatin film was first stimulated in the course of a comparative study of the effect on human tissues of absorbable sponges and various plastic materials. As the result of these studies we felt that the film might be used as an aid in the closure of troublesome pleural defects. This report presents our experience with gelatin film used in this capacity.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director, who assumes no responsibility for the statements made or the conclusions drawn by the authors.

1. Barnes, A. C.: The Use of Gelatin Foam Sponges in Obstetrics and Gynecology, Am. J. Obst. & Gynec. **54**:105-107 (July) 1947. Buchman, J., and Blair, J. E.: The Use of Absorbable Substances to Obliterate Bone Cavities and as Hemostatic Agents in Operative Procedures on Bones and Joints, J. Bone & Joint Surg. **29**:650-658 (July) 1947. Cloward, R. B., and Cunningham, E. B.: The Use of Gelatin Sponge in Prevention and Treatment of Cerebrospinal Rhinorrhea, J. Neurosurg. **4**:519-525 (Nov.) 1947. Cope, B. A., and Hipskind, M. M.: Use of New Agents in the Treatment of Epistaxis, Eye, Ear, Nose & Throat Monthly **26**:417-419 (Aug.) 1947. Correll, J. T., and Wise, E. C.: The Stability of Thrombin Penicillin or Streptomycin in the Presence of Gelatin Sponge, Oxidized Cellulose, or Each Other, Surg., Gynec. & Obst. **85**:211-213 (Aug.) 1947. Ficarra, B. J., and Lionello, J.: Use of Fibrin Foam in Gallbladder Fossa Following Cholecystectomy, New York State J. Med. **47**:1606 (July 15) 1947. Jampolis, R. W.; Jenkins, H. P.; Newman, M. M., and Nardi, G. L.: Control of Hemorrhage from the Cardiac Auricles by the Gelatin Sponge: An Experimental Study, Surgery **22**:198-208 (Aug.) 1947. Jenkins, H. P., and Janda, R.: Studies on Use of Gelatin Sponge or Foam as Hemostatic Agent in Experimental Liver Resections and Injuries to Large Veins, Ann. Surg. **124**:952-961 (Nov.) 1946. Jenkins, H. P.; Senz, E.; Owen, H., and Jampolis, R. W.: Control of Arterial Hemorrhage by a Gelatin Sponge "Cuff" and Chronic Surgical Gut Sheath: A New Experimental Method, Arch. Surg. **55**:637-649 (Dec.) 1947. Jenkins, H. P.; Owen, H.; Senz, E.,

(Footnote continued on next page)

The gelatin film[2] used was supplied in sheets of 4 by 5 inches (10.16 by 12.7 cm.), sterilized in appropriate paper packets. The film is slightly thicker than common cellophane. It can be cut with ease to any desired size or shape. It is pliable and can be sewn, although because of its brittleness it is readily torn. Its pliability increases when moistened, and it assumes a rubbery consistency if immersed in water at room temperature.

METHOD OF STUDY

Two groups of patients were studied. In one group the gelatin film was implanted (1 by 2 inch [2.54 by 5.08 cm.] strips) into normal intermuscular fascial planes of 20 patients undergoing operation for other reasons. At varying intervals of time, incident to subsequent surgical procedures, the implants were removed. At the time of removal the gross appearance of the film, if still present, and the surrounding tissue reaction were studied and photographed. Section of the removed areas of implantation were prepared for pathologic examination. From these preliminary studies it was found that the film is nonpyrogenic and apparently nonantigenic and disappears from human tissues in eight to fourteen days. It was, therefore, felt that it might be safely and effectively used as an aid in the repair of pleural defects.

In the second group of patients the gelatin film was employed in a series of patients as an aid in closing pleural defects which could not be closed by simple suture. The operations performed on these patients were as follows: (1) fourteen first stage posterior thoracoplasties in the upper region of the chest in which the pleura was accidentally torn; (2) two extrapleural procedures in which pleural defects due to extension of inflammatory processes from pleura to chest wall were encountered, and (3) seven thoracotomies, which consisted of three pneumonectomies for

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and Jampolis, R. W.: Control of Hemorrhage from Wounds of the Heart by the Gelatin Sponge "Patch" Technique: A New Experimental Method, Am. J. Surg. **126**:973-989 (Dec.) 1947. Laufman, H., and Method, H.: Effects of Absorbable Foreign Substance on Bowel Anastomosis, Surg., Gynec. & Obst. **86**:669-673 (June) 1948. MacDonald, S. A., and Matthews, W. H.: Fibrin Foam and Gelfoam in Experimental Kidney Wounds, J. Urol. **57**:802-811 (May) 1947. MacDonald, S. A., and Powell, R. E.: Gelfoam Hemostasis in Prostatic Surgery, J. Urol. **57**:812-815 (May) 1947. Olwin, J. H., and Wahl, F. J.: The Effect of Absorbable Sponge Materials on the Activity of Thrombin, Surg., Gynec. & Obst. **86**:203-212 (Feb.) 1948. Pruitt, M. C.: Primary Post-Operative Hemostatic Prophylactic Dressing in Anorectal Surgery, Am. J. Surg. **75**:292-295 (June) 1947. Small, J. T.; Clagett, O. T., and Grindlay, J. H.: Additional Use of Gelatin Foam in Thoracic Surgery: Preliminary Report, Proc. Staff Meet., Mayo Clin. **22**:585-589 (Dec. 24) 1947. Rosser, C.: New Hemostatic Dressing in Anorectal Surgery, South. M. J. **39**:921-925 (Dec.) 1946.

2. The kind used was gelfoam film,® supplied by the Upjohn Company, Kalamazoo, Mich.

bronchogenic carcinoma in which large portions of the chest wall or mediastinal pleura were concomitantly removed, one mediastinotomy for removal of a thymoma, one lobectomy in which pleural approximation could not be obtained at the posterior angle of the posterolateral incision and two exploratory thoracotomies with large areas of visceral pleura containing multiple pulmonary fistula resulting from mobilization of the lung.

The film was placed over the pleural defect, and although it adheres fairly well to the surfaces of wounds it was anchored in place over the defect by means of small interrupted black silk sutures.

In the 14 patients who underwent thoracoplasty the area of pleural repair was examined at a subsequent operation. Two of the patients subjected to thoracotomy were examined subsequently at necropsy (eight and twenty-one days respectively), and the area of implantation was excised and examined.

FINDINGS AND COMMENT

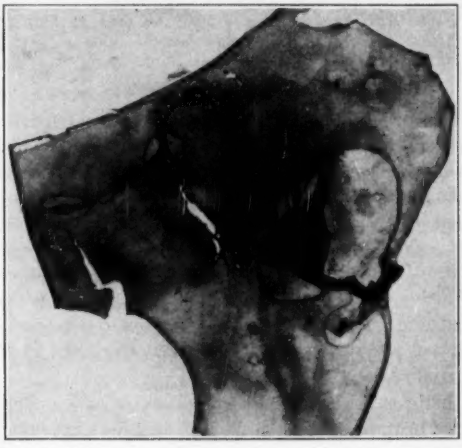
In the first group of patients the gelatin film was found to be completely absorbed between the eighth to the fourteenth day after implantation in wounds. Gross inspection revealed a slight to moderate scar tissue reaction around the area after absorption of the implant. Pathologic sections of the area revealed a moderate foreign body reaction, fibroblastic activity and minimal monocytic and lymphocytic reaction. Some variation in reaction was noted, depending on the time interval and individual susceptibility. In no instance was there evidence of abscess formation. The early and late reactions to this material are considered minimal when compared to the reactions caused by all the other substances studied.

In the patients undergoing thoracoplasty in whom pleural defects were repaired by means of gelatin film, the area was inspected during the secondary stage operation, and it was difficult to tell definitely where the previous defect had been. However, this was identified by means of the black silk sutures which had been used to anchor the gelatin film. Apparently, the pleura grew underneath the gelatin film and the area of defect was closed by a combination of fibrous tissue and pleural growth. The impression on gross examination was that there might be a greater fibrous tissue response in the area of the implantation of gelatin film than elsewhere in the subscapular space. It was considered that the gelatin film had been a valuable aid in the closure of the pleural defects and that the changes occurring secondarily as the result of the film would not be detrimental.

In the 2 cases of extrapleural procedures in which the gelatin film was used, it was felt that it had served as a useful adjunct. One patient had undergone extrapleural pneumothorax and the pleural tear was covered

with gelatin film. There was no evidence postoperatively of an intrapleural pneumothorax, and as the patient progressed in the course of healing after the operation, the fluid level which developed in the extrapleural space during the first ten days remained confined to that space and there was no unusual reaction noted in the extrapleural area. In the other case extrapleural plombage with lucite® was carried out in which a pleural defect encountered during operation was closed with gelatin film. There was no evidence postoperatively of an intrapleural pneumothorax. In both these cases the gelatin film again had provided a satisfactory method of closing the pleural defect.

In all the thoracotomies in which the gelatin film was used there were no effects noted which might contraindicate its use and in all cases it



Photograph of gelfoam® removed at necropsy eight days after its use in repair of pleural defect resulting from removal of the thymoma.

was a valuable aid in the closure of the pleural defects that were encountered. Two of these came to necropsy. One involved a patient who died eight days after mediastinotomy for removal of a thymoma. In the course of the thymectomy it was necessary to remove a large segment of the mediastinal and left anterior parietal pleura because of the fact that the thymic tumor extended into the left pleural space below the arch of the aorta. After removal of the tumor this pleural defect was closed by means of suturing a piece of gelatin film over the area to the surrounding pleura. The patient died eight days postoperatively from respiratory failure in spite of the fact that he had been placed in a mechanical respirator. The accompanying photograph shows the gelatin film which

was removed from this patient at autopsy. The defect that had been present in the pleural sac was almost completely replaced by a thin, fibrous membrane. The gelatin film was stripped with great difficulty from this area, and it was seen that there had been patchy absorption. Pneumothorax was present in this case postoperatively, but it was of a minimal degree, and we did not feel that it was clinically significant nor did it contribute to the ultimate outcome in this patient. In the other case which came to autopsy a pneumonectomy was performed for bronchogenic carcinoma, and it was necessary to remove a good portion of the pericardium and most of the mediastinal pleura along with many of the mediastinal glands. At operation we found it impossible to place pleura over the bronchial stump and the mediastinal structures, and therefore a piece of gelatin film was used to cover this area. The patient died twenty-one days postoperatively as the result of complications probably unrelated to the thoracic procedure. At necropsy the mediastinal structures were found to be covered by a thin, fibrous film and the gelatin film had been completely absorbed, although the black silk sutures which had been used to anchor it were in evidence to identify the area of previous implantation. Apparently the mediastinal pleural edges had grown across the gelatin film bridge to cover the defect over the bronchial stump.

It therefore has been our experience that gelatin film may be a valuable surgical adjunct in some cases as an aid in closing pleural defects. It has a number of disadvantages, however, the chief of these being the fact that the film is absorbed in a relatively short period and the brittle character which at times makes it rather troublesome to handle. It is expected that a more durable and perhaps handier form of this film may be available in the near future.

SUMMARY

Gelatin film was implanted into the normal intermuscular fascial plane in 20 patients, and subsequent examination of the implant was possible. Complete absorption of the film took place in eight to fourteen days, with only minimal foreign body, fibroblastic and cellular reaction noted pathologically in the implanted area. The film has also been of value in the closure of pleural defects, with no detrimental effects noted on the pleural regeneration or the thoracic contents.

BENIGN TUMORS OF THE ESOPHAGUS

Report of a Case of Leiomyoma

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AND
W. E. ADAMS, M.D.
CHICAGO

BENIGN tumor of the esophagus is a rare disease. In the University Clinics of the University of Chicago only 2 cases were found clinically from July 1936 to July 1947; in contrast to this figure, during the same period of time 246 cases of carcinoma of the esophagus were seen. The first case of benign tumor was found during an exploratory thoracotomy for diaphragmatic hernia and was reported by Schafer and Kittle in 1947. The second case was discovered during a routine physical examination, and it is herewith presented.

REPORT OF CASE

A white man, a university student aged 25, had no symptoms whatsoever referable to the esophageal tract or the chest except for rare heartburn after a large meal. In November 1946 he took a physical examination in the university's health office. A routine microfilm of the chest revealed a tumor in the upper mediastinal region. The patient was admitted to the hospital for detailed studies. Physical examination revealed a healthy young man without any defect. Roentgenographic and fluoroscopic examinations of the chest revealed a sharply defined round mass measuring about 9 by 6 cm. situated in the right side of the mediastinum at the level of the branching of the ascending limb of the aorta from the aortic arch (fig. 1). It was in close relation with the esophagus and distorted it considerably. Barium passed through the esophagus smoothly without showing any intramural change. The shape of the superior margin of the esophageal distortion suggested to the roentgenologist the possibility of intramural tumor of the esophagus, but a cyst of the mediastinum could not be ruled out. Bronchoscopic examination showed that the carina was twice the normal width and seemed pushed to the left. There was no bronchial obstruction, and the bronchial mucosa was normal. Esophagoscopy revealed a mass at the level of 24 cm. from the incisure teeth, and this mass pushed the anterior wall of the esophagus posteriorly to the right. Its mucous membrane was normal.

Exploratory thoracotomy was performed on April 4, 1947, under ether and ethylene-oxygen positive pressure anesthesia. The right sixth rib was resected through a long incision over it, and the pleural cavity was opened. A hard, nodular tumor somewhat irregular in contour, measuring approximately 2½ to 3 inches (6.35 to 7.62 cm.) in diameter, was found extending upward from the level of the azygos vein. On mobilization of the esophagus in this region, the tumor was found to be arising from the wall of the esophagus. Only a relatively small portion of the esophageal wall lying posteriorly was free of the tumor. Therefore,

From the Department of Surgery of the University of Chicago.

it was thought inadvisable to remove the tumor, inasmuch as there would be insufficient wall to close the defect. It was thought best to remove the tumor at a later date, from the left side of the chest. After material was taken for biopsy the pleural cavity was closed. Biopsy revealed leiomyoma.

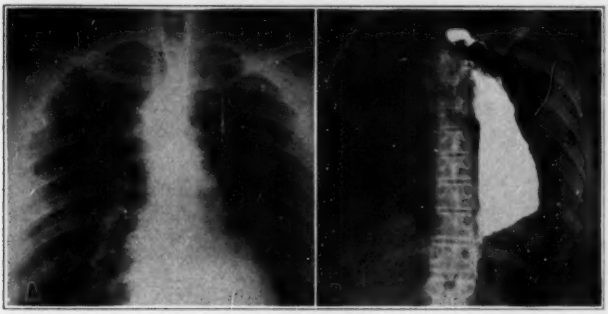

Fig. 1.—*A*, roentgenogram of chest showing mediastinal shadow extending to the right at the level of the aortic arch. Note smooth, curved, sharply outlined border of shadow which was located in the posterior mediastinum. *B*, appearance after operation. Most of the stomach is suspended in the left side of the chest, the anastomosis with the esophagus being at the apex of the pleural space.

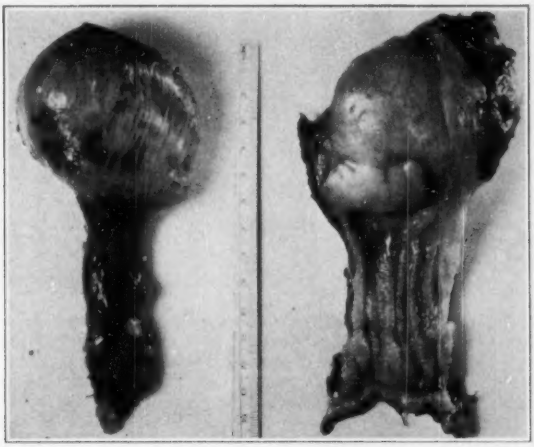

Fig. 2.—Photograph of resected specimen before and after opening the esophagus. Note smooth, rounded tumor occupying approximately two thirds of the wall of the esophagus.

After the patient recovered from the first operation, the second operation was done on May 13, with the same kind of anesthesia as that used before. Through

a long incision over the left eighth rib extending upward posteriorly, this rib and short segments of the seventh, sixth, fifth and fourth ribs were removed. The pleural cavity was entered along this line. The entire thoracic region of the esophagus was mobilized, the tumor being located opposite to and above the arch of the aorta. The diaphragm was opened and the stomach was mobilized sufficiently to enable it to be elevated to the apex of the left pleural cavity. This was accomplished by division of the vasa brevia and the vascular supply along the greater and lesser curvatures and division of the left gastric vessels. The esophagus was divided at its junction with the cardia, the latter being closed with two rows of chromic O surgical sutures. The esophagus was then brought out above the arch of the aorta and mobilized to the apex of the thoracic cavity. The tumor

Fig. 3.—Low power microscopic section showing relation of tumor to structures of the esophageal wall. *T* indicates tumor, M_1 muscle and M_2 mucosa.

was removed, and the stomach was anastomosed with the upper cut end of the esophagus by means of two rows of Pagenstecher sutures. The stomach was secured in this position with interrupted sutures to the pleura. The diaphragm was closed about the stomach, and the thoracic wall was closed. A Pezzer catheter was brought out through the ninth intercostal space posteriorly for drainage.

The patient recovered from the operation gradually. A small encapsulated empyema developed in the upper left region of the chest, which healed on drainage. At present the patient enjoys his normal daily life.

Fig. 4.—High power microscopic appearance of tumor, showing interlacing smooth muscle fibers and cells.

The pathologic specimen consisted of the terminal 18 cm. of the esophagus, weighing 128 Gm. At the proximal end there was a tumor mass, 7½ by 3½ by 8 cm., which was yellow and firm. It seemed to lie beneath the mucosa of the esophagus, and the mucosa was not eroded or ulcerated over the tumor. The tumor involved about two thirds of the circumference of the esophageal wall. It was well encapsulated but had several knoblike projections. The esophagus below it was grossly normal. There were no lymph nodes attached to the specimen

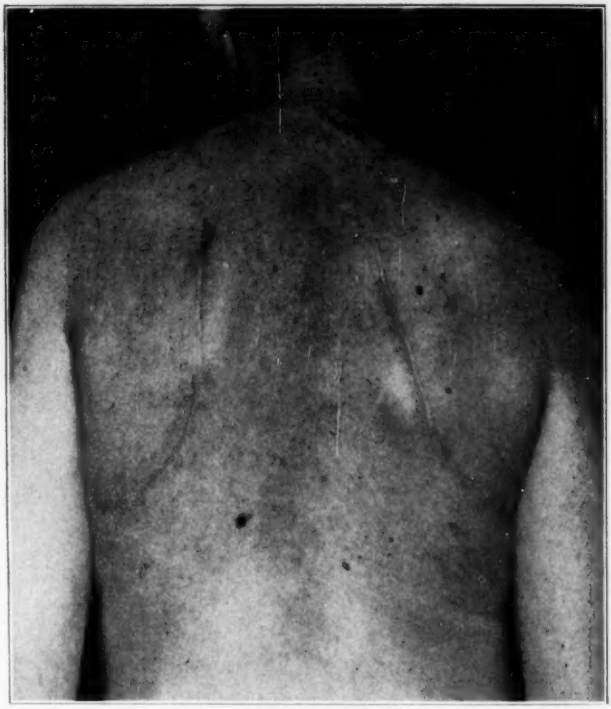

Fig. 5.—Photograph of patient showing location of incisions of the two operations.

(fig. 2). Microscopically, the tumor consisted of interlacing smooth muscle fibers, notably compact in some areas (figs. 3 and 4). It was well vascularized, with many small capillaries. The nuclei and the muscle fibers were larger and lighter in staining than the normal bundles of the muscularis of the esophagus. Although the tumor was not truly encapsulated, the muscle fibers on its surface seemed to be arranged compactly, forming a pseudocapsule.

REVIEW OF THE LITERATURE

Schafer and Kittle reviewed 6,001 autopsy cases in these clinics and found only 11 cases of benign tumor of the esophagus. Since their report, an additional 300 autopsy cases were reviewed, and no more were discovered. Moersch and Harrington, of the Mayo Clinic, found 44 cases in 7,459 autopsy records.

Patterson collected 62 cases of various kinds of benign tumor of the esophagus reported between 1712 and 1932, and Adams and Hoover

TABLE 1.—*Reports of Benign Tumors of Esophagus of Various Types Collected from 1712 to 1948*

	Patterson's Collection, 1712 to 1932	Rose's Collection, 1797 to 1932	Adams and Hoover Collection, 1932 to 1943	Autopsies at Mayo Clinic	Autopsies at University of Chicago	Other Cases Collected by Authors Before 1944	Cases Reported 1944 to 1948	Total
Aberrant thyroid	1	..	..	..	..	..	..	1
Adenoma	2	..	1	..	..	..	..	3
Benign giant cell tumor	..	..	1	..	..	..	..	1
Cyst	4	..	2	2	3	1 †	1 **	13
Fibroma	2	..	5	..	..	..	2 ††	9
Fibrolipoma	..	..	..	..	..	..	1 **	1
Hemangioma	1	..	..	3	..	..	1 ‡‡	5
Lipoma	2	..	3	..	..	1 ‡	1 **	7
Myoma (total)	15	49	2	32	8	4	7	102 *
Fibromyoma	..	..	..	..	..	1 †	1 §§	2
Leiomyoma	6	..	..	32	6	2 §	6 ¶¶	46 *
Lipomyoma	1	..	..	..	..	..	..	1
Myoma	8	..	2	..	2	1 ¶	..	5 *
Mucocele	..	..	..	1	..	..	..	1
Myxofibroma	1	..	..	..	..	..	1 **	2
Neurofibroma	..	..	1	1	..	1 ‖	..	3
Osteochrondroma	..	..	1	..	..	..	..	1
Papilloma	8	..	1	3	..	..	..	12
Polyps	26	..	9	2	..	2 #	2 **	41
Possible myoma	..	..	..	..	..	..	4 ##	4
Unclassified	..	..	3	..	..	..	..	3
Total	62	49	29	44	11	9	20	299 *

* The number of the myoma of Patterson's collection is not included.
† Sauerbruch and O'Shaughnessy.
‡ Nunzi.
§ Grunberger and Pijper; Miller.
¶ Ohsawa.
‖ Komblum and Bradshaw.
Dickes and others; Schelgachew.
** Moersch and Harrington.
†† Cummings.
‡‡ Ferguson and Hackworth.
§§ Harper.
¶¶ Calmenson and Clagett; Harper and Tiscenco; Kentworthy and Welch; Moersch and Harrington; Schafer and Kittle.
Harper; Moersch and Harrington.

collected 29 cases between 1933 and 1943. After searching the literature we found that the reports vary in regard to the incidence of the tumors. It is impossible to determine accurately the number of

cases reported. For instance, Rose in 1936 was able to collect 49 cases of myoma of the esophagus between 1797 and 1932. This number was several times that of Patterson's collection (15 cases of myoma) and yet did not include all reported cases.

From table 1 it is evident that the myoma is the most frequent benign tumor of the esophagus. This agrees with statements of Rose and of Moersch and Harrington. Whereas in the early days several authors thought that polyps were the most frequent, this error can be explained by the fact that the myoma is a comparatively symptom-free tumor and cannot usually be detected clinically. Of his 49 cases, Rose found only 6 in which there were symptoms referable to the esophagus. Four of the tumors were pedunculated; the remaining two were of considerable size and showed a tendency to encircle the esophagus. In the Mayo Clinic, Moersch and Harrington found 2 cases in which there was definite microscopic evidence of myoma and 3 cases of probable myoma with symptoms of esophageal disturbance, in contrast to 32 autopsy cases in which there were no symptoms. In our series of ten myomas of the esophagus, none gave rise to esophageal disturbances. Among 102 collected cases, only 16 patients had symptoms. Of these, 14 had dysphagia, which varied from mild and transient to severe, while 5 died of starvation (Grunberger and Pijper; Rose). Three patients had pain behind the sternum or the xiphoid. Two had occasional epigastric pain. Two gave a history of vomiting, 1 had indigestion and 1 experienced pain radiating to the back. Two cases were complicated by ulcerations which led to the preoperative diagnosis of carcinoma of the esophagus (Brock; Kentworthy and Welch). Another case was complicated by staphylococcic infection from bronchopneumonia shortly before death from that cause (Miller). It should be pointed out that in some reports the histories were not given in many cases or were not complete. Thus, it is impossible to make any statistical conclusions.

Samson and Zelman in 1942 reviewed 26 cases of reported polyps and found only 3 cases in which there were no symptoms. These 3 cases were found at autopsy. The chief complaints of the patients were dysphagia, vomiting, presence of tumor, cough, dyspnea, hoarseness and asthma. In 1 case sudden death resulted from regurgitation of the tumor and blockage of the larynx.

Treatment of benign tumors of the esophagus in the early days consisted of endoscopic removal, gastrostomy when the dysphagia was marked and cervical esophagotomy when the tumor was situated in the cervical portion. Radium and roentgen treatments had been tried but were effective only in cases of hemangioma (Ferguson and Hackworth; Vinson, Moore and Bowing). Gradually, with the advent of

TABLE 2.—*Reported Cases of Benign Tumor of Esophagus Treated Surgically Through the Chest and Abdomen*

Author, Year	Year of Operation	Age	Sex	Preoperative Diagnosis	Operation	Site of Tumor	Nature of Tumor	Result	Comment
Ohsawa, 1933	....	43	F	Idiopathic cardiospasm	Enucleation (route?)	Cardiac end	Submucous myoma	.....	
						Lower third	Fibromyoma	..... Recovery	
Sauerbruch, 1937	1933	33	M	Peptic ulcer of stomach (had exploratory laparotomy once)	Excision of tumor, closure of the esophageal defect; esophagogastrostomy, transpleural				
Sauerbruch, 1937	1931	13	M	Cardiospasm	Dissection from the muscular bed, transpleural	5 cm. above cardiac end	Epithelial cyst (embryonic)	Recovery	
Churchill, 1937	Not given	19	F	Leiomyoma of esophagus or cyst of mediastinum	Enucleation, transpleural	Middle third at D 5 to D 8	Neurofibroma	Not given	
Churchill, 1940	Not given	42	M	Leiomyoma or benign cyst; gumma cannot be ruled out	Enucleation, transpleural	Middle third at D 5 to D 9	Congenital epithelial cyst	Not given	3 doses of roentgen rays before operation
Barrett, 1940	Not given	66	F	Tumor of esophagus or dermoid of mediastinum	Thoracotomy on right side only	Middle third	Fibroma	Died	
Komblum and Bradshaw, 1941	1940	14	F	Neoplasm of esophagus	Gastrostomy first; Torek's operation, transpleural	3 cm. above the diaphragm	Neurofibroma	Died	High voltage roentgen therapy before operation
Schatzki and Hawes, 1942	Not given	26	F	Intramural leiomyoma or neurofibroma	Enucleation, transpleural	Middle third at D 8	Bronchogenic cyst	Not given	600 r before operation
Brock, 1942	1942	47	M	Carcinoma of esophagus	Combined transpleural and abdominal resection	Cardiac end	Myoma	Recovery	
Adams and Hoover	1942	41	F	Benign tumor	Gastrostomy first; transpleural esophagotomy, ligation of the pedicle and cutting	Middle third	Fibroma	Recovery	
Harrington and Moersch, 1944	1943	42	M	Tumor of esophagus	Right transpleural esophagotomy, ligation of the pedicle and cutting	Pedicle at the introitus	Polypoid lipoma	Recovery	
Harrington and Moersch, 1944	1943	56	F	Intramural leiomyoma	Subdiaphragmatic partial resection of esophagus and stomach	Cardiac ends of esophagus and sternum	Leiomyoma	Recovery	
Harrington and Moersch, 1944	1943	39	F	Tumor of esophagus	Transpleural enucleation from esophagus and pericardium	At bifurcation of bronchi	Cyst	Recovery	
Harrington and Moersch, 1944	1943	39	M	Asthma; chronic bronchitis; tumor of esophagus	Transpleural esophagectomy and esophagogastrostomy	Lower 5 in. (12.7cm.) of esophagus	Leiomyoma	Died	
Harper and Tisceneo, 1945	Not given	41	M	Leiomyoma	Transpleural resection and esophagogastrostomy	Middle third	Leiomyoma	Died	
Harper, 1945	Not given	28	M	Tumor of esophagus	Transpleural esophagotomy	Middle third	Fibromyoma	Not given	
Calmenson and Clagett	1946	52	M	Tumor of esophagus	Transpleural esophagotomy	Middle third	Leiomyoma	Recovery	Two tumors
Schafer and Kittle	1946	48	M	Diaphragmatic hernia	Transpleural excision of tumor and partial esophagectomy; repair of hernia	Cardiac end	Leiomyoma	Recovery	
Kentworthy and Welch, 1948	Not given	56	F	Carcinoma of esophagus and stomach	Transthoracic resection of the cardiac portion of esophagus and stomach; esophagogastrostomy	Cardiac end of esophagus	Leiomyoma	Recovery	
Chi and Adams, 1948	1947	25	M	Tumor of esophagus or cyst of mediastinum	Transpleural esophagectomy and esophagogastrostomy	Upper third of thoracic portion of the esophagus	Leiomyoma	Recovery	

thoracic surgery, more radical treatment was employed. Table 2 represents a collection of cases of benign tumor treated by the transpleural and intra-abdominal routes.

SUMMARY

A case of leiomyoma of the upper third of the thoracic portion of the esophagus is reported. Transpleural esophagectomy and esophagogastrostomy were successfully done. A review of the literature on the incidence of benign tumors of the esophagus and the symptoms of myoma of the esophagus was made. Reported cases of benign tumor of the esophagus treated surgically through the chest and abdomen and the results are presented.

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INTRAPERITONEAL DRIP FOR POSTOPERATIVE ADMINISTRATION OF FLUIDS

Preliminary Report

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ALL THE customary methods of parenteral administration of fluids are subject to a certain criticism.

The most popular procedure, venoclysis, necessitates the immobilization of one of the extremities. This is tiresome for the patient, especially if a large amount of fluid is introduced, is likely to disturb his sleep and interfere with movements and change of position of the body, so desirable for prevention of postoperative thrombosis and embolism. Immobilization of infants requires sandbags and restraints and even then cannot always be easily accomplished. Difficulty may be experienced in locating or entering the vein, especially in infants, patients in shock with collapsed blood vessels, obese persons or those in whom the most accessible veins have been used repeatedly and have become thrombosed. If a needle slips out of the vein, the painful procedure of reinsertion is required. If the mishap occurs at night, it disturbs the patient's sleep and causes a loss of valuable time if the intern's service cannot be immediately secured. If the fact that the needle came out of the vein is not promptly noticed, a painful subcutaneous accumulation of fluids results.

In general the same criticism can be directed toward the use of the intra-arterial route, which so far has had little clinical application.

The main disadvantage of hypodermoclysis is the pain connected with it and the difficulty of administering large amounts of fluids. Furthermore, this route is satisfactory for crystalloids but not for the more important colloids. The patient is handicapped in exercising his extremities during the hypodermoclysis and is reluctant to move them after they become distended with fluid.

This study was supported by a grant from the Abbott Laboratories, North Chicago, Ill., which also generously supplied all the fluids used in the experiments.

Intraosseous administration of fluids into the sternum or the tibia is useful in selected cases but requires familiarity with a special technic, not infrequently must be discontinued because the needle becomes occluded, is fraught with a certain danger of perforation of the sternum or osteomyelitis and greatly limits movements of the body.

Proctoclysis lost its popularity because there are doubts as to the absorbability of fluids given in this manner and because many patients cannot retain the solution.

Such drawbacks of the customary methods of parenteral administration of fluids suggested to the authors the employment of the intraperitoneal route in the form of a drip through a tube inserted into the abdominal cavity at the end of the laparotomy, just before the peritoneum is closed.

Theoretically the following advantages of the intraperitoneal drip may be visualized:

1. The patient is spared the pain connected with the introduction of a needle into the vein and the discomfort of having one of his extremities immobilized.

2. There is no interference with the frequent change of position and movements of the extremities, desirable for prevention of pulmonary complications and postoperative thrombosis and embolism.

3. Early ambulation is possible because fluids can be administered with the patient in a sitting position.

4. Less supervision is necessary as compared with other methods of parenteral administration of fluids. Personnel skilled in introduction of a needle into the vein is not required, and a nurse familiar with the aseptic technic can supervise the flow of fluid. This feature is particularly valuable in wartime or on any other occasion when there is a shortage of personnel.

5. There is no danger of a sudden overloading of the circulatory system by a rapid increase in blood volume.

6. The drip does not interfere with other therapeutic procedures such as administration of enemas, or alcohol rubs.

Such alluring features of the intraperitoneal drip are counterbalanced by several important questions:

1. Does the tube cause formation of adhesions, and do they interfere with the infusion?

2. What is the likelihood of an infection?

3. Is the absorption rate of the fluid such as to allow administration of the required amount within a given time?

4. Is there any interference with the healing process?

It is a well known fact that attempts to drain the peritoneal cavity are usually doomed to failure, because the drains often become encapsulated or plugged within a short time. However, it was assumed that the hydrostatic pressure of the fluid injected would maintain the tube patent.

A fair absorption of injected fluids may be expected because the surface of the peritoneal lining is large. According to Wegner's estimation,[1] it covers in man 2,592 sq. cm. The area of the peritoneal surfaces (both parietal and visceral) is about equal to that of the surface area of the body.

The rapidity of absorption of fluids from the peritoneal cavity is shown by experiments of Dandy and Rowntree.[2] They found that 40 to 60 per cent of a phenolphthalein solution was absorbed in one hour. Hertzler [3] stated that if the amount of fluid injected does not exceed 10 per cent of the animal's body weight, 30 per cent of the fluid will be absorbed in the first half hour and at the end of two hours less than 30 per cent will remain.

Intraperitoneal administration of fluids has been recommended by numerous pediatricians. Blackfan and Maxcy [4] introduced intraperitoneal injections of isotonic sodium chloride solution into the treatment of dehydration in infants, on the suggestion of Howland, who saw them employed by Professor Garrod at St. Bartholomew's Hospital in London. McLean [5] and others suggested the administration of dextrose by the same route, and Sanford and Heitmeyer [6] reported beneficial effect of such treatments. Grulee and Sanford [7] reported the use of iron, Platou [8] of diphtheria antitoxin and Rosenberg [9] of neoarsphenamine intraperitoneally. Stewart [10] recommended this method for administration of sodium chloride, Ringer and isotonic sodium-r-lactate solutions. Ponfick and others [11] injected defibrinated blood, with good results.

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The infrequency of complications from puncture of the bowel during intraperitoneal injections is well appreciated. Kistler [12] found in experimental animals that simple penetration of the wall of the bowel by needle did no damage and the perforation healed quickly. Ravenel [13] reported 2 cases of puncture of a nonobliterated hypogastric artery. The dearth of evidence of injury to the abdominal viscera recorded in the literature allows the conclusion that such injections may be performed with relative impunity.

The intraperitoneal route has been abandoned by the majority of pediatricians because (1) there was a potential danger of infection, (2) isotonic sodium chloride solution sometimes irritated the peritoneum and (3) the use of the scalp veins and fontanelles and other procedures have proved more satisfactory.

Recently interest in the peritoneal lining has been renewed by Balazs and Rosenak,[14] Haam and Fine,[15] Abbott and Shea [16] and others who employ peritoneal lavage in the treatment of acute uremia. The procedure is based on the observation that equilibrium between crystalloids of the interstitial fluids is established rapidly when various isotonic fluids are injected into the abdomen.

A careful search of the literature failed to reveal any attempts to introduce fluids intraperitoneally by the drip method. The advantage of a drip over a rapid injection of a fluid is a slower and more uniform absorption and the avoidance of irritation of the peritoneum or any untoward effect on the plastic exudate which may form after the operation and may be washed away by the fluids. The introduction of antibiotics gave hope that the danger of infection may be eliminated. Furthermore, the tube is placed in the abdominal cavity just before closure of the peritoneum, and thus any potential danger of injury to the intestines by a trocar is avoided.

To test the effectiveness of the intraperitoneal drip, a series of experiments was performed on rabbits and dogs. It was decided to point the rubber tube toward the pelvic cavity to get away from the omentum as far as possible. The position of the tip of the tube in the pelvis, far from the diaphragm, does not inhibit the absorption because the theory that the stomas in the diaphragm play a main role in absorption has been largely given up. There is general agreement

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that solutions introduced into the abdominal cavity are absorbed with equal rapidity by all parts of the peritoneum, which acts like a semipermeable membrane, and pass in large part directly into the blood stream. A small amount is probably absorbed through the lymph vessels. Three processes seem to be essential for the absorption—osmosis, diffusion and the physiologic activity of the peritoneum.

The investigation of the value of intraperitoneal drip consisted of (1) employment of various fluids customarily used for parenteral administration, (2) determination of the absorption rate of various fluids, (3) detection of adhesions, if any, (4) selection of the most suitable tubing material, (5) detection of infection, if any, at autopsies and in cultures and (6) study of the prophylactic value of antibiotics.

The rabbits were anesthetized with an intravenous injection of a 3 per cent solution of pentobarbital sodium, 0.5 cc. per pound of body weight. Under aseptic conditions a T tube, size 10, a rubber catheter of the same diameter or a tube made of a synthetic material called tygon,® [17] was introduced through a short midline incision into the abdominal cavity and pushed in a downward direction to bring the outlet away from the omentum. The wound was closed in three layers with cotton sutures, and infusion was started immediately or on the first postoperative day. A similar procedure was employed in dogs.

The following solutions were used for the drip: (1) 5 per cent dextrose in distilled water; (2) isotonic sodium chloride solution, (3) protein hydrolysate,[18] (4) a vitamin mixture [19] containing thiamine, riboflavin and nicotinamide, (5) a vitamin mixture [20] containing thiamine, riboflavin, nicotinamide, pyridoxine and calcium pantothenate, (6) pooled human plasma, (7) penicillin in 5 per cent dextrose, normal sodium chloride solution or aminosol® respectively.

As a rule, each rabbit was given the drip on three or four successive days, 20 to 25 cc. per pound of body weight each time. All dogs, their weight ranging from 18 to 25 pounds (8.2 to 11.3 Kg.), were given arbitrarily 250 cc. per day. The rate of the drip was regulated so that 60 to 80 drops were given per minute. When the drip was finished,

17. Manufactured by the U. S. Stoneware Co., Akron, Ohio, and supplied by the Abbott Laboratories, North Chicago, Ill.

18. Abbott's aminosol® 5% with dextrose 5%, containing 50 Gm. of amino acids and peptides per liter.

19. Abbott's beclysyl,® containing dextrose, 50 Gm.; thiamine, 10 mg.; riboflavin, 5 mg., and nicotinamide, 50 mg. per liter.

20. Abbott's bejectal,® containing thiamine, 10 mg.; riboflavin, 2 mg.; nicotinamide, 30 mg.; pyridoxine, 10 mg., and calcium pantothenate, 10 mg., per 10 cc. Two and a half cubic centimeters of this mixture was added to each 50 cc. of isotonic sodium chloride solution used for the drip.

the end of the tube protruding from the abdomen was folded, covered with a sterile sponge, tied with a string and tucked under the dressing. The animals were given the customary food during the entire duration of the experiment.

Water was offered one group of animals and withheld from the other to enhance the absorption. The animals were killed at specified times after the last drip, and postmortem examinations were done. The peritoneal cavity was inspected for the presence of adhesions or any other signs of irritation; cultures were made, and if there was any fluid left in the abdominal cavity it was aspirated, measured and the sediment studied under the microscope.

As a rule, injections were given on successive days, but occasionally a one to three days' interruption took place. The containers of fluids were connected with the rubber tube inserted into the peritoneal cavity by means of disposable tubing.

To test the effect of the intraperitoneal drip on the healing process within the abdominal cavity, partial gastrectomy, gastroenterostomy and the Mann-Williamson operation were performed on 4 dogs. In the last-mentioned operation, usually performed in order to produce a peptic ulcer, the pylorus is sectioned and the duodenal end closed, the jejunum is also sectioned, and its proximal end is anastomosed to the ileum while the distal end is connected with the stomach. This operation was selected because it offered the opportunity to study the effect, if any, of the intraperitoneal drip on the reparative process following operations on the upper as well as the lower region of the abdomen.

SUMMARY OF THE METHODS IN THE EXPERIMENT

Isotonic sodium chloride solution was administered intraperitoneally to 6 rabbits, 5 per cent dextrose in distilled water to 5 rabbits and 5 per cent dextrose solution in isotonic sodium chloride solution to 1 rabbit. Amino acids in the form of an intraperitoneal drip were given to 9 rabbits (aminosol,* 8; parenamine,* 1) and vitamins to 6 (beclysyl,* 4; bejectal* in sodium chloride solution, 2). Penicillin in isotonic sodium chloride solution was injected into 2 rabbits, penicillin in aminosol* into 1 and penicillin in dextrose into 2, while 1 rabbit was given injections of penicillin in sodium chloride solution with addition of bejectal,* and 2 rabbits injections of human plasma. Fluorescein was injected in 1 rabbit.

The intraperitoneal drip was employed in 4 dogs, each receiving one of the following solutions: isotonic sodium chloride solution with penicillin, dextrose with penicillin, distilled water with penicillin and distilled water with pencillin and bejectal.* The total amount injected each time was 250 cc., containing 25,000 units of penicillin.

The Mann-Williamson operation was performed on 2 dogs, 1 serving as a control and the other receiving isotonic sodium chloride solution with penicillin by means of intraperitoneal drip. A gastroenterostomy was done on 1 dog, which subsequently was given 5 per cent dextrose with penicillin in intraperitoneal drip. A gastric resection was performed on 1 dog, followed by 5 per cent dextrose with penicillin and bejectal® in intraperitoneal drip.

RESULTS

The experiments on rabbits and dogs showed that isotonic sodium chloride solution, 5 per cent dextrose in distilled water, two vitamin compounds (beclysyl® and bejectal®) and penicillin were well tolerated by the peritoneum.

The average absorption of isotonic sodium chloride solution by the peritoneum of rabbits was 40 per cent in two hours and 50 per cent in three hours. The absorption of 5 per cent dextrose in distilled water ranged from 80 to 84 per cent in four hours. The absorption of beclysyl® ranged from 50 to 66.6 per cent in three hours. The entire amount of isotonic sodium chloride solution with addition of bejectal® was absorbed in six hours. The absorption of penicillin in isotonic sodium chloride solution ranged from 77.8 to 88.8 per cent in six hours. Penicillin in 5 per cent dextrose was absorbed at the rate of 28.6 to 55.5 per cent in six hours. The absorption of isotonic sodium chloride solution with addition of penicillin and bejectal® ranged from 77.8 to 100 per cent in six hours.

In some instances, for unknown reasons, the fluid injected intraperitoneally was not absorbed at all. This happened once after the injection of isotonic sodium chloride solution, once after the administration of beclysyl® in isotonic sodium chloride solution, once after the use of dextrose and twice after the injection of penicillin in dextrose.

While such failure to absorb fluids was observed only in exceptional cases when the aforementioned liquids were administered, it was the rule when amino acids were used. Practically the entire amount of amino acids injected could be recovered from the peritoneal cavity six hours later.

The early start of absorption could be demonstrated by the addition of fluorescein to isotonic sodium chloride solution; within two minutes after the start of the drip the conjunctivas, ears and the tip of the rabbit's nose assumed a greenish tint.

Twenty-eight per cent of dextrose with penicillin administered to a dog was absorbed in four hours. Eighty per cent of distilled water with addition of penicillin and bejectal® was absorbed by 1 dog in four hours.

Ninety per cent isotonic sodium chloride solution with penicillin was absorbed by 1 dog in four hours. Another dog absorbed 80 per cent of distilled water with penicillin in four hours.

In the great majority of cases omentum was found wrapped around the portion of the tube located within the abdominal cavity. In some instances fibrinous deposits were present on the parietal peritoneum around the tube. However, no interference with the drip was ever encountered.

Amino acids were apparently not absorbed at all. The abdomen opened six hours after the last injection was filled with fluid, and numerous fibrinous deposits were found all over the parietal and visceral peritoneum.

Pooled human plasma was apparently not absorbed. No signs of irritation of the peritoneum were present, but the abdomen was filled with fluid six hours after the last injection.

All agar cultures were negative except in two or three cases, in which contamination in all probability was responsible for the presence of a few colonies of staphylococci. The inspection of the abdominal cavity in those few cases failed to reveal any signs of peritonitis.

The fluid obtained from the peritoneal cavity of rabbits which had been given injections of amino acids contained albumin and coagulated in the test tube within a few minutes.

After administration of all other fluids except amino acids the sediment of centrifuged specimens contained numerous white and red blood corpuscles and a few epithelial cells.

Six rabbits died after the fourth injection of amino acids, 1 after the first injection of 5 per cent dextrose in isotonic sodium chloride solution and 1 after one injection of beclysyl® in isotonic sodium chloride solution.

The postmortem examination failed to reveal any signs of inflammation of the peritoneum in rabbits and dogs, with the exception of rabbits in which fibrinous deposits developed after injection of amino acids.

COMMENT

All fluids with exception of amino acids and pooled human plasma were absorbed fairly rapidly by rabbits and dogs.

Withholding of water by mouth during the experiment accelerated the rate of absorption.

The fact that amino acids were not absorbed at all contraindicates their use for intraperitoneal drip.

The danger of infection of the peritoneum is apparently minimal if the customary precautions are taken. Even without addition of penicillin no infection could be demonstrated at the postmortem examinations or on cultures.

The omentum, which in many instances was wrapped around the peritoneum, and the scattered fibrinous deposits did not interfere with the intraperitoneal drip. Even an interval of two days between the injections did not produce any occlusion of the outlet of the tubing.

The use of tygon® tubing material in preference to rubber catheters offers the advantage of a smaller diameter, great tensile strength and the ease of removal due to the slippery surface.

Inasmuch as, according to the prevailing opinion, the greatest part of solutions absorbed from the peritoneal cavity passes directly into the blood stream, it appears that intraperitoneal drip would be indicated in instances in which a venoclysis otherwise would be employed. The employment of this route allows of a reduction of the amount of fluid to be given by other means. The exclusive use of the intraperitoneal drip may come into consideration for patients in whom obesity, shock or extensive burns of extremities make superficial veins inaccessible.

As stated previously, withholding of water by mouth accelerated the absorption of fluids by the peritoneum in animals. Inasmuch as the intraperitoneal drip would be used in man during the early postoperative period when little or nothing is taken by mouth and some degree of dehydration may be present, a satisfactory absorption of fluids by the peritoneum may be expected.

General peritonitis, ascites of whatever origin, extensive postoperative adhesions or multiple metastasis of malignant tumors may be considered contraindications to the intraperitoneal drip.

We assiduously avoid drawing any dogmatic conclusion that the intraperitoneal route is to be used to the exclusion of other methods of parenteral administration of fluids. The intraperitoneal drip, however, may either substitute for or supplement other methods by offering an easy and apparently innocuous way of supplying the necessary fluids.

Two problems require further investigations: (1) Do inflammatory processes constitute a contraindication to the intraperitoneal drip, either because they may interfere with absorption or because this method may contribute to the spread of the infection? (2) If the intraperitoneal drip is to be used after surgical procedures other than laparotomies, can administration be done safely through a needle or a trocar?

SUMMARY

The following preparations were injected intraperitoneally in rabbits through a rubber or a synthetic tube in the form of a drip: isotonic sodium chloride solution, 5 per cent dextrose amino acids, vitamin compounds, plasma and penicillin. All solutions with the exception of amino acids and human plasma were absorbed more or less rapidly and were well tolerated by the rabbits. Isotonic sodium chloride solution

with penicillin, dextrose with penicillin and distilled water with penicillin were injected intraperitoneally in dogs. All solutions were well tolerated and more or less rapidly absorbed.

Postmortem examinations and cultures failed to reveal any signs of infection in rabbits and dogs.

Fibrinous deposits or omentum found wrapped around the portion of the tube protruding into the peritoneal cavity did not interfere with the drip.

The intraperitoneal drip had no untoward effect on the healing process after the Mann-Williamson operation, gastrectomy or gastroenterosotomy in dogs.

The findings suggest the employment of intraperitoneal drip in man as a supplement to or a substitute for venoclysis.

The addition of penicillin to the fluid administered intraperitoneally is recommended as a prophylactic measure.

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TREATMENT OF CHRONIC OSTEOMYELITIS WITH PENICILLIN AND PRIMARY CLOSURE OF OPERATIVE WOUNDS

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TREATMENT OF CHRONIC OSTEOMYELITIS WITH PENICILLIN

A PRELIMINARY report of the treatment of chronic osteomyelitis, published in 1944, by members of the Evans Memorial and Massachusetts Memorial Hospital (Keefer and others; Anderson, Howard and Rammelkamp) demonstrated that penicillin was an effective antibiotic agent in the treatment of this disease but that when it was employed in combination with surgical intervention the results were much more satisfactory and permanent.

The following report represents a study of the end results obtained in from one to six years, ending March 1948, and does not include any new patients treated in the last twelve months.

The penicillin was used (1) without surgical intervention in 32 patients and (2) with surgical intervention and primary closure of operative wounds in 55 patients.

1. *Treatment Without Surgical Intervention in 32 Patients.*—Before discussing the treatment of chronic osteomyelitis by means of surgical intervention, it seems appropriate first to report on patients who were treated with penicillin but were not operated on.

Read at the Boston Orthopedic Club, April 1948.

From the Robert Dawson Evans Memorial of the Massachusetts Memorial Hospitals and the departments of medicine and orthopedic surgery, Boston University School of Medicine.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

Thirty-two patients were thus treated, many of them when penicillin was first released for study and when the amount was limited and the dosage, of necessity, much lower than that now used. Some patients received as little as 5,000 to 10,000 units, and then, as the supply became greater, the dosage was increased to 25,000 or 50,000 units and in several cases to 100,000 units every three hours intramuscularly.

Inadequate dosage in the earlier cases undoubtedly accounted for a number of the failures, but enough patients received what today is considered an adequate dosage to make this report of some value.

The results in general appeared to be satisfactory at first, but many patients showed relapse and a recurrence of symptoms, which clearly demonstrated that penicillin alone would not solve the problem of chronic osteomyelitis, though in a number of the patients who showed relapse symptoms could be eliminated by additional treatment with systemic administration of penicillin.

Recurrence of symptoms after healing frequently was preceded by local trauma, which apparently liberated encysted bacteria into a fresh hematoma, causing reactivation of the disease process. Repeated systemic administration of penicillin would eliminate or control these symptoms for an indefinite period, but the end results were unsatisfactory in the majority of the cases.

Most of the patients gained weight, in many instances to the extent of 20 to 40 pounds (9.1 to 18.1 Kg.), and showed marked improvement.

Thirty-two patients were treated with penicillin only, and of this group 1 died within eighteen hours of his admission to the hospital. He had arrived unconscious and in a moribund condition and did not respond to a heavy dosage of penicillin. This death was recorded in an earlier paper (Anderson and others). In 5 other patients the wound never healed. In 26 patients healing occurred, and of these 15 had a relapse after healing. Only 11 of the 32 patients remained healed with systemic administration of penicillin only. Of the other 20, 8 received no more treatment at our hospital, though in some of these healing occurred after additional surgical procedures and penicillin therapy at other institutions at a later date. Twelve others of this group remained healed after penicillin therapy and surgical intervention, and these are included in the group to be discussed in the chapters on treatment by means of operation.

These statistics determined our future course in operating on all patients suffering from chronic osteomyelitis who were able to withstand the necessary procedures.

Also, some patients who arrived at the hospital badly depleted by this disease were given penicillin and general medical treatment until they became good surgical risks.

2. *Treatment With Surgical Intervention and Primary Closure of Operative Wounds in 55 Patients.*—A review of the probable causes of failure or recurrence of symptoms after apparent recovery from operation prior to admission or after treatment with penicillin alone may be summarized as follows:

1. Some organisms become resistant to penicillin.

2. All unremoved sequestrums, regardless of size or location, have a tendency to reactivate osteomyelitis. They should be removed.

3. Scar tissue often contains sequestrums which are too small and of insufficient density to be demonstrable in roentgenograms. Moreover, scar tissue within bone cavities or outside of bone often contains viable bacteria encysted within it, and trauma of this scar tissue often reactivates the disease. All scar tissue should be excised.

4. Unhealthy granulation tissue harbors bacteria within bone and scar tissue and in sinus tracts, even though the latter may remain closed for many years. All granulation tissue and all sinus tracts should be excised.

TABLE 1.—*Final Results in 32 Patients Treated with Penicillin Only*

Died	1
Never healed	5
Healed	26
Healed and relapsed	15
Remain healed	11

5. Osteomyelitic cavities within sclerosed bone have impaired blood supply, which may prevent adequate local distribution of penicillin, administered systemically. Therefore, all bone cavities known to harbor infection should be opened and curetted thoroughly.

A review of our 55 cases showed that in some the disease in easily accessible areas had been eradicated but that in others a complete dissection adjacent to or about large blood vessels and nerves had been avoided, which permitted scar and granulation tissue, sequestrums and sinuses to remain. These conditions probably accounted for a great number of years of drainage, suffering and humiliation.

The efficiency of penicillin warranted the conclusion that when all diseased tissue which could be safely removed was excised and when adequate dosage of penicillin was employed the wound might be closed, providing a high concentration of penicillin could be maintained locally within the wound for the first ten or fifteen days and an adequate systemic dosage of penicillin continued as long as might appear necessary in individual cases.

It was to be expected that if the whole area of the wound were kept sterile throughout the healing process, recovery might be permanent.

This proved to be true whenever all the aforementioned principles were completely carried out and the surgical technic about to be detailed was adequately and thoroughly performed. All failures were due to resistance of the organism to penicillin or to inadequate surgical treatment or to both. Occasionally it was impossible to perform all the surgical procedures desired because of the condition of the patient, or because of technical difficulties presented by certain anatomic areas. In rare cases to have removed all diseased bone might have produced a fracture which would have complicated and delayed recovery.

SURGICAL PROCEDURE

A procedure which left the operative area a closed system with administration of penicillin (Anderson and others) was used.

Preoperative Care and Study.—On the patient's admission to the hospital, the following preoperative studies are made and medical care given.

1. Good preoperative roentgenograms are made in appropriate planes.

2. Material from wounds or sinus tracts is cultured, and organisms isolated are studied for resistance to penicillin to determine adequate dosage for systemic administration.

3. Adequate systemic administration of penicillin is instituted, the doses to be repeated at three hour intervals. The average for the early cases is 25,000 to 50,000 units and for the later cases 100,000 units.

4. Into the sinuses is injected iodized poppyseed oil 40 per cent, with the patient on the x-ray table, and fresh roentgenograms are taken to demonstrate the course and ramifications of the sinuses in relation to bone and soft tissue (fig. 1).

5. Operation is delayed until there is adequate concentration of the drug to minimize spread of the disease elsewhere by the operative procedure.

6. The usual careful preoperative local preparation of the area under consideration is carried out.

Operation.—After surgical preparation on the operation table, methylene blue is injected into sinuses, if present, so that their course may be determined, to facilitate complete excision. An adequate incision is made to afford thorough exposure of the area of disease and to accomplish the necessary procedures without undue forcible retraction of soft tissues. As exact hemostasis as possible is maintained throughout the operation. Accepted anatomic approaches are used, but sinuses do not respect anatomy; therefore, often it is necessary to follow tortuous paths in order to excise them completely.

All sequestrums are removed (figs. 1, 2, 3, 4, 5, 6 and 7). As much scar tissue as can be safely removed is excised. Material from the depths of the wound is cultured for further study.

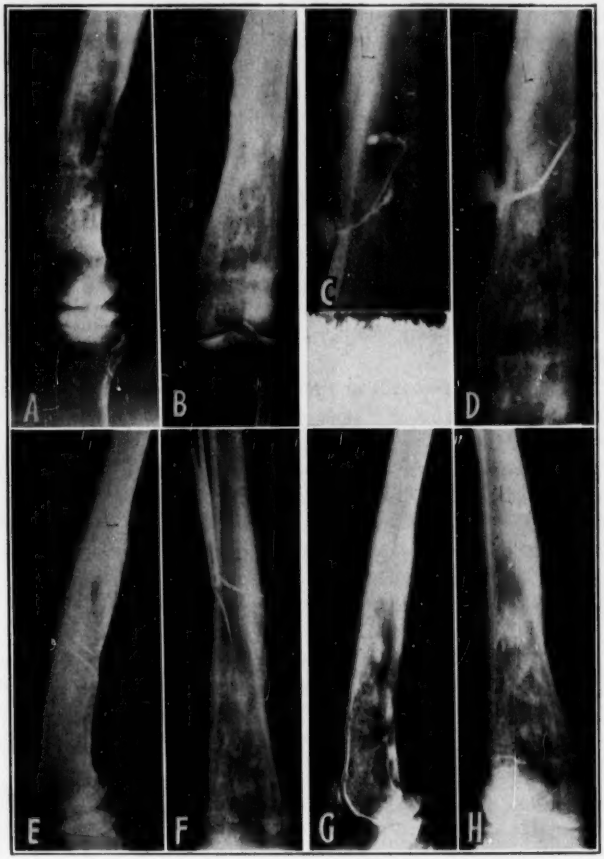

Fig. 1.—Anteroposterior and lateral views of the femur in a boy aged 17 with osteomyelitis of two years' duration. Healing occurred seventeen days after operation. *A* and *B*, preoperative views; *C* and *D*, views showing iodized poppyseed oil in sinus tracts; *E* and *F*, views after sequestrectomy, showing penicillin catheters in place; *G* and *H*, views four years later.

A bone window of adequate size is made to permit thorough sequestrectomy and removal of granulation tissue and scar tissue. The bone

is not saucerized as in the Orr treatment. Only enough healthy bone is removed to permit carrying out all the principles mentioned. The bone edges are made smooth, and throughout the operation great care

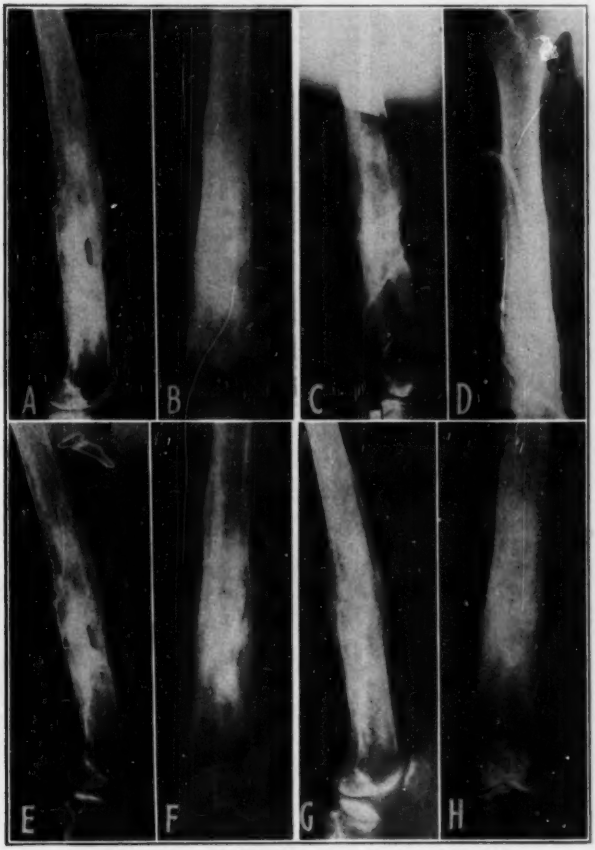

Fig. 2.—Osteomyelitis of the femur of twenty-four years' duration in a woman aged 36. Healing occurred fifteen days after operation. *A* and *B*, anteroposterior and lateral views showing sequestrums and bone cavity; *C* and *D*, postoperative views showing sequestrectomy and penicillin catheters; *E* and *F*, condition one year later; *G* and *H*, condition five years later.

is taken not to leave any bone chips or sand *in situ* (figs. 1, 2, 3, 4, 5, 6 and 7).

When excision of all diseased tissue is completed, the wound is irrigated with normal isotonic sodium chloride solution and suction apparatus is utilized to remove this and all fine particles of bone sand,

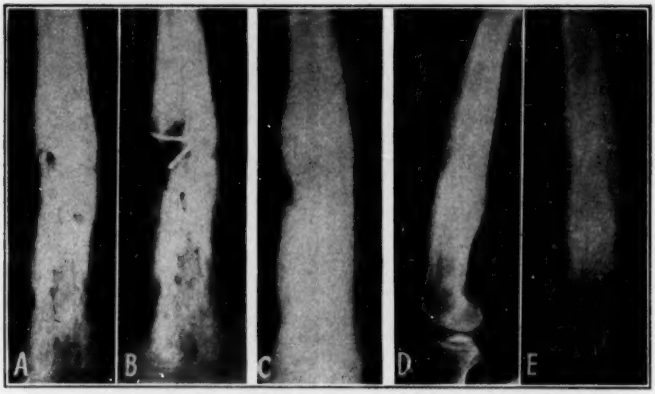

Fig. 3.—Osteomyelitis of the femur of four months' duration in a boy aged 14. Healing occurred forty-one days after operation. *A*, anteroposterior view showing extent of disease and sequestrums; *B*, anteroposterior view after sequestrectomy with penicillin catheter in place; *C*, anteroposterior view showing condition one year later; *D* and *E*, anteroposterior and lateral views five years later (patient is now on college wrestling team).

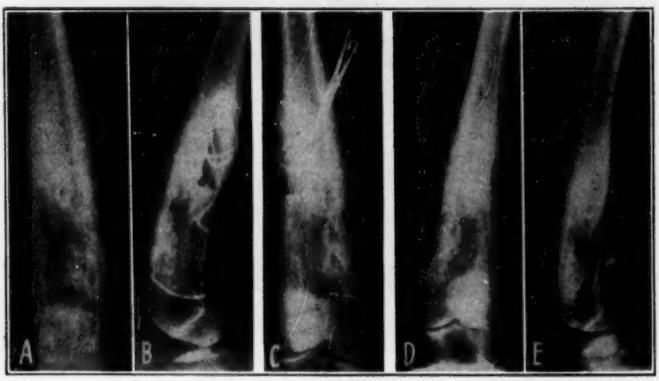

Fig. 4.—Osteomyelitis of the femur of two years' duration in a boy aged 17. Healing occurred twenty-one days after operation. *A*, anteroposterior view showing sequestrums and diseased area; *B* and *C*, anteroposterior and lateral views after sequestrectomy, showing type of bone windows for sequestrectomy; *D* and *E*, condition five years later.

which may act as irritants and reactivating factors if left in any part of the wound.

One or more fine soft rubber catheters are inserted in the deeper portions of the bone and wound cavity and sutured to the skin for postoperative administration of penicillin—not for drainage (figs. 1, 2, 3 and 4).

The wound is accurately closed in anatomic layers, and a large, bulky, soft sterile dressing is applied, with catheters protruding. The ends of the catheters are clamped with small hemostats and covered with sterile gauze.

This method of closure, with catheters for penicillin only and not for drainage, makes the operative area a relatively closed system, with

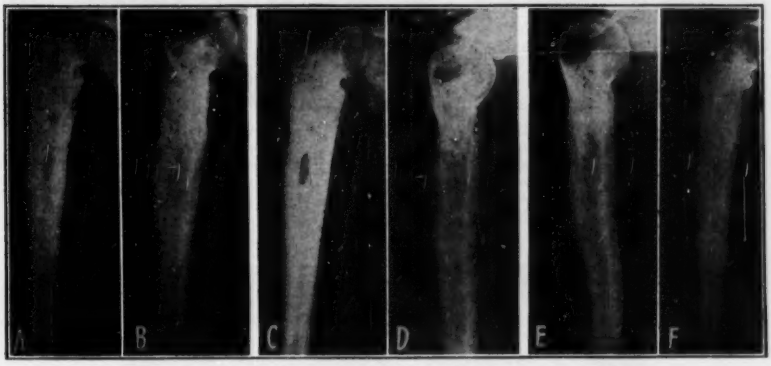

Fig. 5.—Osteomyelitis of the humerus of ten months' duration. Healing occurred fifteen days after operation. *A* and *B*, anteroposterior and lateral views showing sequestrum and bone cavities; *C* and *D*, anteroposterior and lateral views one year after sequestrectomy; *E* and *F*, condition four years after operation.

penicillin reaching it continuously through the capillary bed as the result of systemic administration and intermittently as it is injected through the catheters. This builds up a concentrated dosage of the drug where it is most needed and hastens complete sterility of the whole area of the wound. The more rapid sterilization thus provided hastens opportunity for bone repair (Anderson and others).

Occasionally splints are used to immobilize an extremity, especially if the disease is near a joint.

Postoperative Care.—The usual postoperative supportive treatment is given, including intravenous administration of fluids, one or more transfusions when needed and vitamin therapy.

Immediately after operation, at three hour intervals, the systemic administration of penicillin in appropriate dosage is continued. Also, 25,000 to 50,000 units of penicillin is immediately injected into the

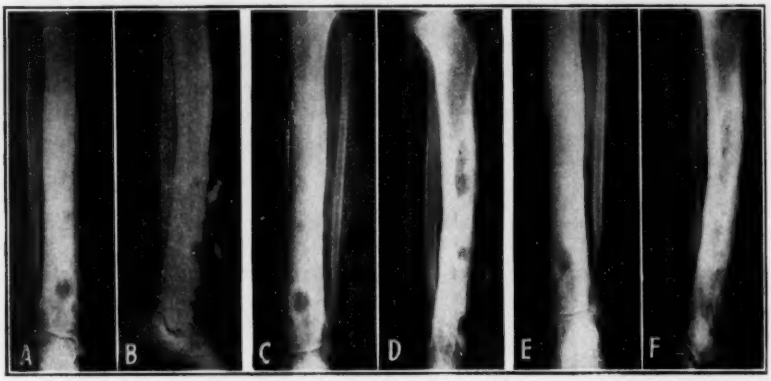

Fig. 6.—Osteomyelitis of the tibia of seven years' duration in a man aged 47. Two operations were performed; healing occurred twenty-three days after operation on the lower area of disease and twenty-four days after operation on the upper area. *A* and *B*, anteroposterior and lateral views showing extent of disease; *C* and *D*, anteroposterior and lateral views after sequestrectomy; *E* and *F*, condition three years later.

Fig. 7.—Osteomyelitis of the femur of seven years' duration in a man aged 41. Healing occurred thirty-three days after operation. *A*, anteroposterior view showing large sequestrum and bone cavities; *B*, condition four years later.

catheters, and this is repeated two or three times daily until they are removed, which may be any time from the tenth to the fourteenth day.

Skin sutures are removed when the wound is well healed, generally from the tenth to the fourteenth day.

Postoperative rest in bed is continued for about two to three weeks after complete healing of the wound in cases in which the lower extremities are involved. Rest in bed for three to ten days when the upper extremities are affected, with the use of a sling for about two to four weeks after healing, is the general rule.

TABLE 2.—*Incidence of Sinus Tracts*

	No. of Bones
Sinus with one or more sequestrums	38
Sinus without sequestrum	12
Sequestrum without sinus	2
Undraining bone abscess	8
Total	60

TABLE 3.—*Results of Operation on 55 Patients (60 Bones Involved)*

Bone	Symptoms Remain	Symptoms Arrested
33 femurs	0	33
7 tibias	1	6
5 humeri	0	5
4 radiuses	0	4
3 ulnas	0	3
3 iliums	0	3
3 spines	0	3
1 clavicle	0	1
1 fibula	0	1
60	1	59

CLINICAL MATERIAL

Fifty-five patients suffering from chronic osteomyelitis have been treated and carefully studied. Sixty major bone structures were involved.

The age varied between 14 and 58 years. The duration of disease varied from three months to fifty-two years, and the average duration of the disease was eleven and one-half years for every bone involved. At the time treatment was begun symptoms and signs of active infection had been present from two weeks to fifty-two years.

Staphylococcus aureus was cultured from local lesions in the 50 cases in which draining occurred. In 2 cases in which sequestrums were present without sinus the wounds were sterile at operation, probably because of the preoperative use of penicillin. At operation the wounds

in 4 of 8 cases with undraining bone abscess were sterile and Staph. aureus was cultured in the other 4.

The total duration of symptoms in these 55 cases exceeded seven hundred years.

Most patients with sinus tracts also had sequestrums, as shown in table 2.

END RESULTS

Eighty-one operations have been performed on sixty bones in 55 patients, with the results shown in table 3.

Recovery on the basis of the number of operations performed is shown in table 4.

USE OF OTHER ANTIBIOTIC AGENTS

The purpose of the study was to determine the efficiency of penicillin plus anatomic layer closure of surgical wounds, begun by this

TABLE 4.—*End Results*

No. of Bones		No. of Operations
47	Remain healed after the first operation	47
8	Remain healed after the second operation	16
1	Remains healed after the third operation	3
1	Never healed after any of three operations	3
1	Remains healed after a fourth operation	4
1	Remained healed after the third operation until relapse caused by automobile accident; recovered without surgical intervention by systemic administration of penicillin	3
1	Healed and then showed relapse after each of four operations; remains healed after fifth operation	5
60	(59 healed; pinpoint drainage in 1)	81

group in 1942. Therefore, other antibiotic agents were used in only 3 patients. In them the infecting organism had become resistant to penicillin as a result of repeated and prolonged penicillin therapy coincident with previous surgical procedures, so that streptomycin was tried. The surgical procedure that has been outlined was employed. The dosage of streptomycin given was 250,000 units every three hours by systemic administration and the same dose locally by catheter two or three times a day.

Two of the patients, each with chronic osteomyelitis of a femur, have remained healed after treatment by this method. The third patient had chronic osteomyelitis of a tibia and was greatly improved. After administration of streptomycin, the streptomycin-sensitive organisms disappeared from his wound but some of the penicillin-resistant organisms remained, and he still has pinpoint drainage. In this case treatment both with penicillin and with streptomycin failed. All 3 patients received only one course of streptomycin therapy.

Results of treatment with penicillin and operation or with streptomycin and operation in this group of 55 patients with chronic osteomyelitis involving sixty bones is shown in table 5.

COMPLICATIONS

The most frequent complications were (1) increasing resistance to penicillin and (2) increased sensitivity to penicillin.

1. *Increasing Resistance to Penicillin.*—It was noted in some patients who had received inadequate surgical treatment or inadequate dosage of penicillin or both, which made repeat operations necessary, that the infecting organisms frequently became considerably resistant to penicillin. Increase of dosage to as high as 100,000 units every three hours systemically and 50,000 to 75,000 units locally three times daily generally overcame this, though such high dosage was rarely necessary.

2. *Increased Sensitivity to Penicillin.*—In some cases hypersensitivity to penicillin developed and urticaria occurred. Oral administration

TABLE 5.—*End Results*

	Penicillin		Streptomycin		Total of Both	
	No. of Patients	No. of Bones	No. of Patients	No. of Bones	No. of Patients	No. of Bones
Healed	52	57	2	2	54	59
Failed	3	3	1	1	1	1

of 50 mg. of diphenhydramine hydrochloride (benadryl hydrochloride®), one to three times a day, frequently gave relief.

RAPIDITY OF BONE REPAIR

In this whole series of patients the degree and rapidity of bone repair and regeneration have been remarkable (Anderson and others). This has been due for the most part to three factors: (1) administration of penicillin; (2) meticulous surgical treatment, and (3) primary closure of all wounds.

The proper use of penicillin both before and after operation has permitted rapid sterilization of the area of disease and thus prevented further disintegration of bone and formation of sequestrums from bone edges and surfaces. Moreover, meticulous attention toward leaving all bone edges and surfaces smooth at the end of operation is important and diminishes the opportunity for formation of sequestrums. Primary closure of wounds has prevented drainage of blood serum, with its valuable calcium content, thus permitting more rapid local deposition of calcium than the Orr or the Trueta method of treatment by which wounds are packed open.

COSMETIC APPEARANCE

Primary layer closure of wounds has another beneficial result. It greatly improves the contour and prevents retraction of scar into bone cavities, which so frequently happens in the Orr and Trueta methods of treatment. Moreover, with the older methods, when retracted scars were present the bone edges often were covered with skin only and, therefore, were sensitive to light pressure.

Primary layer closure in most patients permits normal muscle layer coverage, with much less discomfort when the area is subjected to trauma.

CONCLUSIONS

A high percentage of patients suffering from chronic osteomyelitis may be relieved by a combination of (1) adequate systemic administration of penicillin, (2) excision of all diseased tissue with primary closure of wounds and (3) adequate local administration of penicillin in a closed system as described.

The incidence of recurrence of chronic osteomyelitis is dependent on the amount of diseased and scar tissue left in situ at operation.

STREPTOMYCIN IN CHRONIC TRAUMATIC OSTEOMYELITIS

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CHRONIC traumatic osteomyelitis following injuries of long bones sustained in World War II was one of the most serious problems confronting the army general hospital one year after the cessation of hostilities. At Oliver General Hospital over 300 patients with chronic osteomyelitis were treated from Oct. 1, 1946 to Jan. 1, 1948. Various principles of conservative and surgical management [1] evolved from World War I to the present were applied, with uniformly good results.[2] However, in spite of diligent measures, infection persisted in certain refractory cases. In the present study of 26 such cases, all cases of united fractures, we sought to evaluate the effectiveness of streptomycin with or without the combination of penicillin.[3] Four cases of infection following bone graft and 1 case of chronic hematogenous osteomyelitis were also added. In this series, the average duration of infection was 26.2 months and an average of 3.6 sequestrectomies or saucerizations had been previously performed. Further conservation of bone substance was now of even greater importance than it had been in the earlier

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1. Orr, H. W.: The Treatment of Infected Wounds Without Sutures, Drainage Tubes, or Antiseptic Dressings, J. Bone & Joint Surg. **10**:605-611, 1928; The Development of the Concept of Antisepsis and Asepsis from Lister to World War II, Surg., Gynec. and Obst. **85**:209-224, 1947. Trueta, J.: The Treatment of War Wounds and Fractures, New York, Paul B. Hoeber, Inc. Kelly, R. P.; Rosati, L. M., and Murry, R. A.: Traumatic Osteomyelitis: The Use of Skin Grafts; I. Technic and Results, Ann. Surg. **122**:1-11, 1945; Traumatic Osteomyelitis: The Use of Skin Grafts; I. Technic and Results, ibid. **122**:1-11, 1945; Traumatic Osteomyelitis: The Use of Skin Grafts; II. Subsequent Treatment, ibid. **123**:688-697, 1946. Churchill, E. D.: The Surgical Management of the Wounded in the Mediterranean Theater at the Time of the Fall of Rome, Ann. Surg. **120**:268-283, 1944.

2. Dehne, E.; Smith, W. S., and Ganey, J. B.: Unpublished Data.

3. Lockwood, J. S.; White, W. L., and Murphy, F. D.: The Use of Penicillin in Surgical Infections, Ann. Surg. **120**:311-344, 1944. Lyons, C.: Penicillin Therapy of Surgical Infections in the United States Army, J. A. M. A. **123**:1007-1018 (Dec. 18) 1943.

stage of infection. The use of any therapeutic agent would necessarily be a severe test of its performance in this series. Prior to and after therapy, the patients were observed daily by us for a period of fifteen months. All except 2 had severe battle injuries, the majority of which were incurred from shell fragments. Streptomycin was employed in 31 cases, either alone or in combination with penicillin.

Meleney [4] has already pointed out the difficulty of evaluating drugs in the treatment of established surgical infections. He has described the abscess wall appropriately even though he was undoubtedly speaking of more recent surgical infections: "The wall of an abscess is made up of necrotic tissues and thrombosed blood vessels which may prevent immune elements or medications in the blood from reaching the focus where the organisms are living and carrying on their metabolic process." That the infected area in chronic traumatic osteomyelitis is surrounded by a dense, fibrous tissue of poor vascularity has long been recognized as a definite obstacle to drug therapy. Systemic chemotherapy gives desirable blood and tissue levels except where dense sclerotic tissues act as a barrier. Metallic foreign bodies, clothing, leather from shoes and sequestrums have little opportunity of becoming sterile even if bathed in a saturated solution of a powerful antibiotic. The ideal case for treatment with an antibiotic such as penicillin or streptomycin is one in which foreign bodies and sequestrums are absent and a high local level of the drug can be obtained. Sequestrectomy or saucerization with débridement of the surrounding fibrous tissue removes a barrier, and on purely theoretic grounds susceptible organisms could be attacked with the present powerful antibiotic agents. The chance for complete eradication of infection could further be enhanced by the combination of parenteral and continuous high local levels of the drugs.

Lemphier and Cashman [5] reported 4 cases of chronic traumatic osteomyelitis treated with intramuscular injections of streptomycin combined with 150,000 units three times a day locally over a seven day period. DeBakey and Pulaski [6] stated that 40 per cent of 179 patients with wound infection including chronic traumatic osteitis were "improved" by the use of streptomycin but emphasized that the improvement was coincident with adequate wound revision. They were of the opinion that "sufficient contact of streptomycin with the causative organism must occur infrequently regardless of the route of administration."

4. Meleney, F. L.: The Difficulty of Evaluating Drug Treatment in Surgical Infections, J. A. M. A. **124**:1021-1026 (April 8) 1944.

5. Lemphier, T. A., and Cashman, C.: Treatment of Chronic Osteomyelitis with Streptomycin, New England J. Med. **236**:318-322, 1947.

6. DeBakey, M., and Pulaski, E. J.: An Analysis of the Experience with Streptomycin in the United States Army Hospitals, Surgery **20**:749-761, 1946.

On the other hand, Howes [7] suggested another approach to the local therapy of wounds and recommended the combination of penicillin and streptomycin in order to include a wider bacterial spectrum. The discovery of an enzyme, penicillinase,[8] elaborated by gram-negative bacilli had added a great deal regarding our knowledge of the local chemical treatment of wounds. A method for extraction of the enzyme from penicillin-resistant organisms as well as a method of assay of its activity has been described by McQuarrie.[8b] It has been postulated that penicillinase inhibits the action of penicillin by destroying it and thereby accounts for the poor performance of local penicillin in the presence of gram-negative organisms. Frequently the gram-negative organisms are found in wounds and in time often appear in preponderance, masking the presence of gram-positive organisms. This would tend to explain why the gram-positive organisms thrive when penicillin is employed locally.

Pulaski [9] performed in vitro streptomycin sensitivity studies of the bacterial flora of 143 surgical infections and found that a level of streptomycin of 32 units per cubic centimeter is effective against more than 80 per cent of the gram-negative bacteria and more than 60 per cent of the gram-positive cocci commonly encountered.

Lady Florey [10] and others recently reported an extensive bacteriologic survey of 63 wounds associated with 53 compound comminuted fractures of the tibia incurred in war along with the effectiveness of the local application of certain drugs, including streptomycin, on the gram-negative flora of these wounds. They found that 51 of 56 wounds harbored gram-negative organisms from the second week onward. Their studies further emphasized the importance of serial cultures, although these need not consistently yield the same gram-negative flora "in spite of efforts to swab all parts of the wound." They concluded that streptomycin was the only drug tested which was consistently effective in eliminating gram-negative organisms. Evidence has been presented that gram-negative organisms present more than a nuisance problem in chronic osteomyelitis.[11]

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7. Howes, E. L.: Topical Use of Streptomycin in Wounds, Am. J. Med. **2**:449-456, 1947.

8. (*a*) Abraham, E. P., and Chain, E.: An Enzyme from Bacteria Able to Destroy Penicillin, Nature, London **146**:837, 1940. (*b*) McQuarrie, E. B., and Liebmann, J.: Studies on Penicillinase, Arch. Biochem. **5**:301-315, 1944.

9. Pulaski, E. J.: Streptomycin: Status Report on Its Therapeutic Use, Bull. U. S. Army M. Dept. **6**:565-570, 1946.

10. Florey, M. E.; Ross, R. W. N. L., and Thornton, E. E.: Infection of Wounds with Gram Negative Organisms: Clinical Manifestations and Treatment, Lancet **1**:855-861, 1947.

11. Howes.[7] Florey, Ross and Thornton.[10]

METHOD OF ADMINISTRATION, DURATION OF THERAPY AND DOSAGE

We have followed the recommendation of maintenance of blood levels at 10 to 30 units [12] and have found 400 mg. intramuscularly every four hours to be adequate in most instances. After our earlier experience with intramuscular injections of streptomycin alone, having recognized the fact that a high continuous local level was desirable and observed the disappointing results of the use of intermittent doses of penicillin in old indolent infections, we sought other methods of local administration. Carrel,[13] recognizing the shortcomings of the intermittent topical application of drugs, used a continuous drip in an attempt to obtain high sustained local concentrations of the drug. In applying streptomycin locally, we employed a modification of this technic. First as a clinical trial, 1,000,000 units of streptomycin was placed in 1,000 cc. of isotonic sodium chloride solution and an overhead bottle was prepared for continuous local administration. Sodium chloride solution was preferred as the vehicle because of its known beneficial effects on granulating wounds, even though it rendered the antibiotic perhaps slightly less efficient.[9] The wound was first lined with fine mesh gauze, and a single small rubber catheter was inserted. A gauze pack was made to surround the tube and after the pack was saturated with approximately 100 cc. of the concentrated solution of streptomycin, the preparation was allowed to drip into the wound continuously over a twelve hour period daily. The pack remained undisturbed for intervals of one week. After the first few trials of this method, although drainage did decrease markedly, mild drainage persisted. The dosage was increased to 2,000,000 and then 4,000,000 units of streptomycin daily until a pronounced clinical effect on the wound was noted. High local concentrations of the drug, from 10,000 to 100,000 units per cubic centimeter, have been employed elsewhere.[14]

Since mixed infections with both streptomycin and penicillin-sensitive organisms were found to be relatively common, and the destruction of penicillin by penicillinase, elaborated by the gram-negative bacilli, was borne in mind, penicillin was employed in the manner just described, with 1,000,000 units per thousand cubic centimeters of isotonic sodium chloride solution. The solutions were kept separately and connected by a Y tube to the catheter leading to the wound. The choice of the drug or combination of drugs depended on wound cultures, and in no instance was either streptomycin or penicillin employed unless it was

12. Pulaski, E. J.: Streptomycin Therapy, Bull. U. S. Army M. Dept. **7**:739, 1947.

13. Carrel, A., and Dehelly, G.: Infected Wounds, New York, Paul B. Hoeber, Inc., 1917.

14. Nichols, D. R., and Herrell, W. E.: Streptomycin: Its Clinical Uses and Limitations, J. A. M. A. **132**:200-205 (Sept. 28) 1946.

indicated by the culture. The combination with parenteral injections of streptomycin was used as often as possible.

In this series, administration of streptomycin was continued for an average period of 36.9 days, the shortest being nine days and the longest one hundred and twenty days.

BACTERIOLOGY AND LABORATORY STUDIES

Prior to drug therapy, serial cultures and streptomycin sensitivity tests were done in each instance. The gram-negative organisms (table 1) included Bacillus proteus, Bacilius pyocyaneus, Escherichia coli, Aerobacter aerogenes, Friedländer's bacillus and Salmonella suipestifer. Of these, B. proteus was found more frequently than any other. In two instances Friedländer's bacillus was eliminated from wounds after combined intramuscular and local administration of streptomycin. In 1 of the cases (B. E.) Friedländer's bacillus was found in three cultures prior to streptomycin therapy, and during treatment cultures of the wound made at weekly intervals failed to show any growth of this organism. In this case drainage stopped, and the wound has been dry and free of increased heat, redness or swelling for six months.

In each case routine laboratory studies included complete blood counts, urinalyses and determination of blood streptomycin levels twice weekly. In a majority of cases, vestibular function tests were done before and after streptomycin therapy.

Early laboratory experience with the effect of streptomycin in vitro [15] indicates that the problem of severe degrees of drug fastness may be a major factor in the failure of the drug as applied in certain types of infections. Finland and others [16] have called attention to the rapid development of severe degrees of streptomycin resistance in a number of cases of urinary tract infections. The organisms isolated in 1 of his cases were sensitive to 25 units of streptomycin, while on the fifth day of treatment they were resistant to 50,000 units.

In 1 of our cases, not included in this series because treatment was incomplete at the writing of this paper, studies of streptomycin sensitivity showed B. proteus sensitive to 40 units per cubic centimeter. Eighteen days after therapy, studies of sensitivity showed that B. proteus was inhibited by over 50 units per cubic centimeter. Fifty-nine days after local treatment only, growth of B. proteus was not inhibited by 100,000 units per cubic centimeter. In another case, also not included

15. Buggs, C. W.; Bronstein, B.; Hirschfeld, J. W., and Pilling, M. A.: In Vitro Action of Streptomycin on Bacteria, J. A. M. A. **130**:64-67 (Jan. 12) 1946.

16. Finland, M.; Murray, R.; Harris, H. W.; Kilham, C., and Meads, M.: Development of Streptomycin Resistence During Treatment, J. A. M. A. **132**:16-21 (Sept. 7) 1946.

TABLE 1.—*Responses to Individual Courses of*

Patient	Anatomic Location	Duration of Infection, Mo.	Number of Sequestrectomies or Saucerizations	Days After Operation Streptomycin Initiated	Bacteria of Wound Prior to Therapy	Bacteria of Wound After Completion of Therapy
W. L.	Subtrochanteric region	24	2	0	B. pyocyaneus, E. coli,	Drainage stopped
E. S.	Left femur, pubis	30	4	0	B. proteus	Drainage stopped
N. S.	Right hip	30	6	0	Friedländer's bacillus, B. proteus	Drainage stopped
E. L.	Left knee	16	1	30 before and 60 after operation	B. proteus, hemolytic Staph. albus	Drainage stopped
C. L. (2)	Right hip	27	2	0	B. proteus, Staph. albus	Drainage stopped
C. R. L. (2)	Right knee	34	6	0	B. proteus, nonhemolytic staphylococcus	B. proteus, nonhemolytic staphylococcus
						Within One Month
W. H.	Left tibia	10	2	22	A. aerogenes, beta hemolytic streptococcus, Staph. albus, diphtheroids	Culture showed "no growth" in 48 hours 24 days after onset of therapy
J. E.	Right tibia	28	4	13	Friedländer's bacillus, diphtheroids, nonhemolytic Staph. albus	Nonhemolytic staphylococcus albus
R. E.	Left os calcis	27	4	24	Friedländer's bacillus, nonhemolytic Staph. albus	Drainage stopped
E. P.	Left femur	41	4	13	B. proteus	Drainage stopped
J. R.	Right knee	23	6	7	B. proteus, E. coli	B. proteus, E. coli
						Long Period
C. C.	Left femur	25	3	120	B. proteus, Staph. albus	B. proteus, Staph. albus
J. C.	Left tibia	23	5	136	A. aerogenes, nonhemolytic Staph. albus	A. aerogenes, diphtheroids
W. H.	Left femur	35	3	240	B. proteus, nonhemolytic Staph. albus	B. proteus, nonhemolytic Staph. albus
W. R.	Right femur	20	3	88	B. pyocyaneus, nonhemolytic Staph. albus	B. pyocyaneus, nonhemolytic Staph. albus
W. O.	Right tibia	30	2	133	B. pyocyaneus (gram-positive organisms identified on Gram stain, but overgrowth of B. pyocyaneus prevented culture)	B. pyocyaneus
F. N.	Left lower tibia and talus	20	4	175	Friedländer's bacillus, B. pyocyaneus, staphylococci and streptococci	Friedländer's bacillus, B. pyocyaneus, staphylococci and streptococci

Method of Administration, Dosage and Duration of Therapy	Results
400 mg. intramuscularly every 4 hours for 12 days	After operation and course of streptomycin, drainage stopped; still dry and without evidence of inflammation after 10 months
400 mg. intramuscularly every 4 hours for 30 days	Drainage stopped completely 47 days after operation; still dry after 7 months
400 mg. intramuscularly every 4 hours for 14 days; 4 Gm. streptomycin, 1,000,000 units penicillin locally daily for 57 days	Drainage stopped completely for the first time in 30 months; all discoloration in region of extensive scar disappeared; still dry at the end of 4 months
250 mg. intramuscularly every 3 hours for 120 days	Drainage stopped completely 51 days after therapy discontinued, 83 days after operation (saucerization and arthrodesis)
400 mg. intramuscularly every 4 hours for 14 days; 4 Gm. streptomycin and 1,000,000 units penicillin locally daily for 53 days	No drainage for 6 months; profuse suppuration stopped for the first time in 27 months (see figure 2 and legend)
400 mg. intramuscularly every 4 hours for 27 days	Drainage subsided gradually; streptomycin used as an adjunct to saucerization and arthrodesis; still dry at the end of 4 months (see C. L. [1], knee)
After Operation	
400 mg. intramuscularly every 4 hours for 14 days; 4 Gm. streptomycin, 1,000,000 units penicillin locally daily for 28 days	Drainage stopped completely 60 days after operation although the last 30 days were required for complete epithelization of wound; through and through type of drainage established; still dry after 7 months.
4 Gm. streptomycin, 1,000,000 units penicillin locally daily for 42 days	Friedländer's bacillus not found in three subsequent cultures although cultured on three occasions prior to therapy; discharged from hospital 4 months later with minimal serous drainage
400 mg. intramuscularly every 4 hours for 13 days; 4 Gm. streptomycin and 1,000,000 units penicillin locally daily for 26 days	Seven days after therapy began, culture taken from wound showed no growth after 48 hours; wound filled in rapidly, and there has been no dainage for 4 months.
400 mg. intramuscularly every 4 hours for 14 days; 2 Gm. streptomycin, 1,000,000 units penicillin locally daily for 16 days; dosage of streptomycin increased to 4 Gm. daily for following 16 days	Stopped draining at the end of 32 days (see text); no drainage for 4 months
400 mg. intramuscularly every 4 hours for 30 days	No demonstrable effect noted; this patient underwent combined saucerization and arthrodesis of the knee; operation 9 months later showed retained foreign bodies within two bone abscesses; arthrodesis successful
After Operation	
400 mg. intramuscularly every 4 hours for 26 days	No demonstrable effect noted, but at operation later the previously saucerized cavity was filled with a large amount of granulation tissue and pus and a thick fibrous base; finally treated successfully with débridement and split thickness graft after 3 previous failures elsewhere by the same method
400 mg. intramuscularly every 4 hours for 21 days; 4 Gm. streptomycin, 1,000,000 units penicillin locally daily for 28 days	Rapid pronounced decrease in drainage to 1 drop of serous drainage daily in 1 week; after previous operation, drainage became mechanically trapped under overhanging ledges of bone; while on therapy, these spaces became filled with healthy-appearing granulations and epithelium; discharged from hospital 5 months later with 1 drop of serous drainage daily, due to small epithelial defect
400 mg. intramuscularly every 4 hours for 36 days	Definite "arresting" effect; no drainage for the first time in 35 months; drainage stopped 33 days after onset of therapy; remained dry for 45 days, then repeated mild flare-ups of the infection occurred
400 mg. intramuscularly every 4 hours for 22 days	Drainage stopped 2 days after therapy started; a questionable good result since drainage had been gradually decreasing and operation preceded arrest of infection by 86 days
400 mg. intramuscularly every 4 hours for 26 days	No demonstrable effect noted; at operation a large cavity filled with granulation tissue, pus and dense scar tissue at the base was demonstrated; treated successfully by saucerizations and skin graft and without further antibiotics
400 mg. intramuscularly every 4 hours for 37 days	No demonstrable effect of parenteral administration of streptomycin noted; at operation a large cavity filled with granulation tissue, pus, metallic and fabric foreign bodies demonstrated; 9 months later, patient transferred to amputation center

TABLE 1.—*Responses to Individual Courses of*

Patient	Anatomic Location	Duration of Infection, Mo.	Number of Sequestrectomies or Saucerizations	Days After Operation Streptomycin Initiated	Bacteria of Wound Prior to Therapy	Bacteria of Wound After Completion of Therapy
C. R. L. (1)	Right knee	32	6	206	Friedländer's bacillus, B. proteus	B. proteus, nonhemolytic staphylococcus
D. L.	Right hip, ilium, ischium, pubis	27	2	297	B. proteus, nonhemolytic staphylococci	B. proteus, nonhemolytic staphylococcus
F. E.	Left femur	26	2	313	E. coli, Friedländer's bacillus	Drainage stopped
C. L. (1)	Right hip	25	2	210	B. proteus	Proteus temporarily not cultured from wound
W. W.*	Both femurs, tibias, ulnas, radiuses and humeri	11	1	92	S. sulpestifer, E. coli, A. aerogenes, B. pyocyaneus	Salmonella not cultured in several attempts over one year period following drug therapy
H. S.	Right hip	33	4	111	B. proteus, Friedländer's bacillus	Drainage stopped
W. P.	Right ilium and ischium	26	5	104	B. pyocyaneus, nonhemolytic Staph. aureus	Hemolytic Staph. aureus
I. T.	Left femur	28	4	86	Nonhemolytic Staph. albus, B. pyocyaneus	Drainage stopped
R. G.	Right tibia, right femur	28	5	61	B. proteus, beta hemolytic streptococcus	B. proteus, Friedländer's bacillus
J. L.	Left tibia	29	5	94	B. pyocyaneus, hemolytic Staph. aureus, Friedländer's bacillus	B. pyocyaneus, hemolytic Staph. aureus, Friedländer's bacillus
						Infections Following
J. H.	Right tibia	(After Bone Graft) 3	(Before Bone Graft) 3	104	E. coli, B. pyocyaneus, beta hemolytic streptococcus, nonhemolytic Staph. aureus	B. pyocyaneus, Staph. aureus
P. K.	Left tibia	1	1	35	Friedländer's bacillus, nonhemolytic Staph. albus	Drainage stopped
P. B.	Left femur	3	1	21	B. proteus, E. coli	B. proteus, E. coli
A. M.	Right femur	1	2	31	B. proteus	Drainage stopped

* This patient had chronic hematogenous osteomyelitis.

Method of Administration, Dosage and Duration of Therapy	Results
400 mg. intramuscularly every 4 hours for 32 days	Drainage decreased markedly within 5 days after therapy; no drainage after 7 days of therapy, for the first time in 32 months; remained dry 50 days; radical débridement and arthrodesis followed
400 mg. intramuscularly every 4 hours for 30 days	Failure; drainage temporarily changed from purulent to serous type; studies with iodized poppyseed oil 40 per cent showed ramifying sinus tracts leading to multiple metallic foreign bodies in the region of the acetabulum and pelvis
400 mg. intramuscularly every 4 hours for 14 days; 4 Gm. streptomycin, 1,000,000 units penicillin locally daily for 23 days	Drainage stopped completely 23 days after therapy initiated; no drainage or signs of infection for 7 months (see figure 3)
400 mg. intramuscularly every 4 hours for 32 days	No response to parenteral administration of streptomycin demonstrated; large sequestrum demonstrated later surgically; infection finally controlled by combined sequestrectomy and antibiotics (see C. L. [2])
400 mg. intramuscularly every 4 hours for 44 and later 45 days	No apparent clinical effects on over-all picture 1 year after therapy (see text); after 2 courses of strepytomycin, first cultures from abscesses of both forearms 6 and 12 months later showed no growth after 48 hours of incubation
400 mg. intramuscularly every 4 hours for 19 days	Drainage stopped completely 7 days after use of streptomycin started; therapy started when patient was having an acute exacerbation of his infection, with fever 101 F., local increased heat, redness and severe pain in the hip radiating to the knee; still dry and without signs of inflammation at the end of 5 months; drainage had been continuous for 33 months
400 mg. intramuscularly every 4 hours for 40 days	Drainage stopped 24 days after therapy started; remained dry without any signs of infection for 113 days, followed by a flare-up, with moderate drainage; first culture following flare-up showed hemolytic Staph. aureus (see figure 2)
400 mg. intramuscularly every 4 hours for 9 days; 4 Gm. streptomycin, 1,000,000 units penicillin locally daily for 9 days	Pronounced effect on drainage and appearance of wound in short time; drainage reduced to a few drops of serous fluid, which gradually stopped completely over the next 4 months; long period was required for healing of small epithelial defect
400 mg. intramuscularly every 4 hours for 7 days; 4 Gm. streptomycin, 1,000,000 units penicillin locally daily for 34 days	Pronounced local effect; notable reduction in drainage; wound began to epithelize in 1 week; discharged from hospital 3 months later with minimal serous drainage
400 mg. intramuscularly every 4 hours for 14 days; 4 Gm. streptomycin, 1,000,000 units penicillin locally daily for 37 days	No demonstrable effect with the combined parenteral and local method; inaccessibility of the focus most likely reason for poor clinical effect of the drugs
Bone Grafts	
400 mg. intramuscularly every 4 hours for 26 days	Marked decrease in drainage in 24 hours; drainage increased moderately after cessation of therapy; went on to union but required sequestrectomy at a later date
400 mg. intramuscularly every 4 hours for 21 days	Had three sinuses with fairly profuse drainage after operation; these promptly healed on therapy, the fracture went on to union and drainage stopped; still dry and without signs of infection after 10 months
400 mg. intramuscularly every 4 hours for 48 days	Drainage decreased markedly in 1 week; one or two sinuses promptly healed; still has mild persistent serous drainage 4 months after initiation of therapy; bone graft progressing satisfactorily without evidence of sequestration or bone abscess
400 mg. intramuscularly every 4 hours for 50 days	Drainage decreased markedly in 2 weeks; had previously had two bone grafts; one sinus closed in 2 weeks and the other in 8 weeks; bone graft progressing satisfactorily, and there is no evidence of sequestration or bone abscess 5 months after operation.

here for the same reason, A. aerogenes was sensitive to 50 units per cubic centimeter before treatment, but sixty-four days after treatment growth of the organisms was not inhibited by 50,000 units per cubic centimeter but was inhibited by 100,000 units.

In the cases in which good results were reported with combined administration of penicillin and streptomycin locally, the clinical picture was that of a wound with healthy-appearing granulation tissue, minimal serous drainage and progressive epithelization even after one month of therapy (C. L., B. E., R. G., N. S., J. C., W. H., F. E.). One explanation for the clinical success in spite of the apparent drug fastness is that all or the majority of the clinical improvements resulted from the first two weeks of therapy and that after marked initial improvement the tissues themselves took over the task of coping with the residual organisms.[17]

As Buggs [15] has suggested regarding sensitivity, a different strain of the same organism may have been isolated later, one either resulting from reinfection or not previously cultured. In the latter event, it is believed that while there is a suppression of one strain growth of another strain may be permitted.

RESULTS OF THERAPY

Cases in which there were obvious sequestrums or foreign bodies were not considered suitable for streptomycin therapy although 1 case of hematogenous osteomyelitis with massive sequestration of all the long bones was included in this series. Serial cultures of the wound were taken to determine all organisms present as well as to serve as a check on previous cultures.

In order to facilitate the interpretation of clinical results, division of the uses of streptomycin was made in the following manner: (1) as an adjunct to surgical treatment; (2) administered within one month after operation; (3) administered when a long period had elapsed after operation; (4) given for infections following bone grafts. Group 1 excludes to a large extent the factor of the fibrous tissue barrier in obtaining high local levels. Cases in this group approach the "ideal" for antibiotic therapy. Cases in group 3 were considered surgical failures and therefore exclude the factor of surgical intervention in the success of treatment. Similarly, because of the formation of dense fibrous tissue surrounding the infection, spectacular results could not be anticipated.

The results were designated by the terms "good," "fair," "failure" and "questionable." Results were considered good when drainage and all signs of infection were absent for a period of at least four months.

17. Topley, W. W. C., and Wilson, G. S.: The Principles of Bacteriology and Immunity: Local Immunity, Baltimore, Williams & Wilkens Company, 1936, chap. 50, pp. 924-931.

Fair results were considered to have occurred when (*a*) drainage decreased markedly or (*b*) drainage stopped for the first time in twenty-eight months and remained absent for a month or more. The result was termed a failure when the patient showed no significant response to streptomycin. In 2 cases the results were designated as questionable. In 1 of these (W. R.) there was a mild progressive decrease in drainage after an operative procedure performed eighty-eight days previously while drainage stopped completely two days after initiation of streptomycin. The other (W. W.) was a case of chronic hematogenous osteomyelitis involving all the long bones in which the first several cultures showed pure growth of S. suipestifer. After two courses of streptomycin, culture of spontaneous drainage from the left forearm six months later showed no growth after forty-eight hours. Culture of material from a slowly developing abscess (eight weeks) of the right forearm twelve months after a course of streptomycin also showed no growth. Final

TABLE 2.—*Results of Administration of Streptomycin Relative to the Time of Surgical Intervention*

	Good	Fair	Failure	Questionable	Total
As an adjunct to surgical treatment	6	0	0	0	6
Within one month after surgical treatment	3	1	1	0	5
Long period after surgical treatment	3	5	6	2	16
For infections following bone graft	2	2	0	0	4
Total					31

clinical analysis after one year showed little demonstrable change in the over-all picture that could be attributed to streptomycin.

Table 2 shows the results of administration of streptomycin relative to the time of surgical intervention. The best results were obtained when the drug was used as an adjunct to surgical intervention. This was to be expected inasmuch as, so far as it was possible, the fibrous periphery of the area of infection was removed surgically and this allowed for high local tissue levels of the drug. The role of surgical intervention in these cases was undoubtedly an important one, although in 1 case (C. L.) it was conceded that adequate wound revision was incompletely accomplished. In 6 cases streptomycin was used as an adjunct to surgical treatment, and in all 6 the infections were arrested. In these cases the infection has been arrested for four to nine months.

For the group in which the drug was used within one month after surgical intervention, a brief description of each case is presented. In 1 case (W. H., good) a through and through type of drainage for the leg was necessary, and because of poor results noted with such drainage

in this location it was felt that supplementary antibiotic therapy should be given. In the second case (J. E., fair) a choice between the sacrifice of a large amount of bone substance and trial with antibiotics had to be made. In the third case (B. E., good) the patient had a deep defect involving the os calcis. In the fourth case (E. P., good) there was a sinus tract ramifying from the lateral border of the thigh to the medial aspect of the femur and extending 4 inches (10 cm.) distally, which could not be excised in toto. The fifth patient (J. R., failure) had combined arthrodesis and saucerization of the knee followed two days postoperatively by acute cellulitis of the extremity. In this patient retained foreign bodies bathed in pus and granulation tissue were demonstrated surgically nine months later.

In the group in which streptomycin was given long after operation the problem of fibrosis surrounding the infection must be considered. In spite of this handicap to parenteral therapy, 3 of 16 patients had unquestionably good results. In 3 of the cases with results considered fair the infections were arrested for forty-five, fifty and one hundred and thirteen days with streptomycin therapy for the first time in thirty-five, thirty-two and twenty-six months, respectively. In the remaining 2 cases with results considered fair there was profuse draining prior to combined intramuscular and local therapy with penicillin and streptomycin. In both cases drainage decreased dramatically, followed by healthy-appearing granulations and subsequent epithelization to the extent that the patients could be discharged from the army after a three month period of minimal serous drainage. For 6 of the 16 patients in this group the result was considered a failure. Four of the 6 were subjected to further surgical intervention at a later date. In 1 case (F. N.) retained foreign bodies surrounded by granulation tissue and pus were found. In another case (C. L.) a large sequestrum was demonstrated. In 2 of the cases (W. O. and C. C.), with previous saucerization, the cavities were found to contain a bed of chronic pyogenic granulation tissue with a thick fibrous base. In another case, in which further surgical intervention was not carried out, studies with iodized poppyseed oil 40 per cent outlined a sinus tract leading to multiple metallic fragments.

Good results were obtained in 2 of the 4 cases of infection following bone graft. In 1 case (P. K., good) the bone graft was successful, and at the time of the writing of this paper the other patient (A. M., good) was free from drainage and the graft was progressing satisfactorily; this patient had previously had two unsuccessful bone grafts. In another case (J. H., fair) dramatic response was noted in the amount of drainage following the use of streptomycin; however, on the cessation of therapy, moderate drainage reappeared. Nevertheless, union was accomplished in this case, and it is felt that streptomycin held the infection in check

during its administration. In the fourth case (P. B., fair) drainage decreased markedly and two of the three sinuses promptly healed. At the time of writing this paper, the status of the graft was satisfactory. The patient had already lost one graft by infection.

Table 3 shows a comparison of the results obtained by the parenteral administration of streptomycin alone and the combined parenteral and continuous local administration of streptomycin and penicillin as outlined. Twenty patients were treated by the parenteral method alone, and of these, 7 showed a good response, while in 5 the result was fair and in 6 it was a failure. In 2 cases the result was considered "questionable."

With the combined method, 7 patients showed a good response and 3 a fair response, while in 1 case the result was a failure. In 2 of these cases the antibiotics were used as an adjunct to surgical treatment. In 4 cases the combination was used within a month after the operation.

TABLE 3.—*Results with Streptomycin Alone and with Streptomycin and Penicillin*

	Good	Fair	Failure	Questionable	Total
Parenteral administration of streptomycin alone..	7	5	6	2	20
Combined continuous local administration of streptomycin and penicillin and parenteral administration of streptomycin.....	7	3	1	0	11
Total.....					31

COMMENT

Though the results in our 31 patients treated with streptomycin have not been dramatic, they have nevertheless been encouraging. Investigation of streptomycin in the treatment of bone infections as compared to other infections has been slow. At our disposal we have two of the most powerful antibiotics known to man, and together they are effective against a wide range of bacterial flora, yet there remains the perplexing problem of a method to make these drugs available to the infection.

Several problems are met in this condition which cause difficulty in the treatment with antibiotics. These are (1) decreased vascularity in the region of the infection which renders it difficult to obtain effective levels of the drug, (2) development of resistance of the organisms to streptomycin, (3) determination of dosage and (4) occult foreign bodies or sequestrums.

Since we have shown that there is a definite influence of streptomycin on infections which have been without the benefit of surgical intervention for several months, it is reasonable to assume that this drug can best be

employed immediately after operation, when the local vascular conditions are most favorable to local concentration of the drug.

We have already spoken of the theoretic considerations of combined local and parenteral antibiotic therapy and have reported good results with this method (table 3). In what type of chronic infection involving

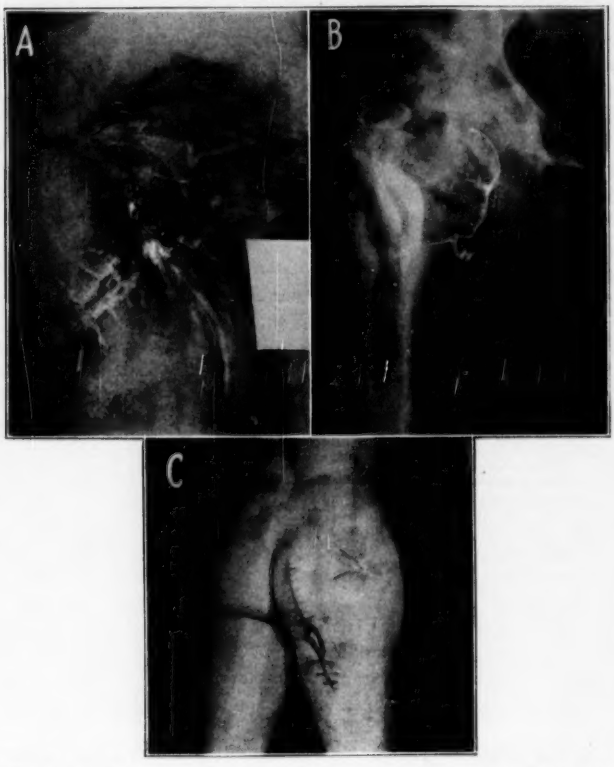

Fig. 1.—*A*, three sinuses in the right groin in the precarious vicinity of the femoral vessels which could not be palpated in the extensive cicatrix. *B*, ankylosis of the hip with apparent sequestration of the head of the femur twenty-seven months after injury. Previous surgical failure due to inability to demonstrate a sequestrum through an anterior approach. *C*, the healed incision used in a posterior approach. The anterior sinuses healed two weeks after operation. Postoperatively, combined intramuscular and local administration of antibiotics was used. Local therapy was used for fifty-three days with minimum drainage, followed by complete cessation of drainage.

bone can this method be employed to the greatest advantage? We have already indicated that the antibiotics may be appropriately used just

after operation. Obviously, in cases in which it is felt that the focus has been eradicated and adequate saucerization has been provided, there would be no great advantage to the topical application of these drugs. However, it must be conceded that in some complex varieties of osteomyelitis [18] (figs. 1, 2 and 3) certain difficulties arise in accomplishing adequate saucerization and elimination of the focus. These are (1) extremely poor anatomic accessibility of the focus (fig. 2), (2) the sacrifice of bone substance to such an extent that the bone is seriously weakened (fig. 3) and (3) the inability to débride and pack the recesses of deep-seated cavities completely even though the foreign bodies or sequestrums are removed (fig. 1). The last requires further elaboration. In our own experience [2] we have found such recesses to har-

Fig. 2.—Extensive intrapelvic sinuses originating in the sacroiliac region and extending into the acetabulum. An extensive anterior approach failed to reach the sinuses at all. Posterior exposure reached the sinuses but did not allow surgically adequate excision beyond the sacral plexus. The patient was given intramuscular injections of streptomycin one hundred and four days after operation, and this was continued for forty days. The infection became arrested fourteen days after administration of the drug was initiated and remained arrested for one hundred and thirteen days, only to recur. This was the first time that the drainage had stopped in twenty-six months.

bor chronic pyogenic granulation tissue which later becomes partially walled off with fibrous elements and eventually becomes the focus of infection and the reason for surgical failure. As the bacterial growth flourishes, the granulations become poorer in quality. Now if the bacterial flora could be kept at a minimum or even eliminated (table 1, W. H., B. E. and J. E.), the chances for eradication of infection would be materially

18. The anatomic considerations are to be presented in another paper from the Orthopaedic Section, Oliver General Hospital.

greater. Figure 1 illustrated this principle well. In the case represented, continuous local administration of streptomycin and penicillin kept bacterial growth at a minimum while healthy granulations filled in the deep-seated cavity. The principles in the treatment of the other two varieties are similar. In a cross section of all the patients treated in the septic division of this hospital, patients with these varieties constituted a small percentage of the total. Continuous local administration of streptomycin and penicillin should prove to be a valuable addition to our armamentarium in combating such infections.

Fig. 3.—Anteroposterior and lateral views show a cavity extending almost completely through the middle of the shaft and accompanying marked sclerosis. Saucerization was not recommended because of the pronounced sclerosis and the danger of pathologic fracture. Combined local and parenteral antibiotic therapy was elected. Therapy was continued for twenty-three days, at which time drainage stopped. The patient has been discharged from the army and has been free from drainage for six months.

In regard to infections following bone grafts the primary consideration is union. In 2 of our cases we have changed the infection from severe to mild and theoretically have rendered the condition a more nearly normal one for osteogenesis. In the other two in which bone grafts were done infection was aborted. It is felt that treatment of

infection is aimed at the tissues surrounding the graft and not at the graft itself. Therefore as soon after operation as infection is recognized would be the optimal time for the administration of the drug before the sclerotic changes that accompany long-standing infection take place.

Since resistance of the organisms to streptomycin develops rapidly, it is likely that higher initial doses, with a shorter duration of therapy, might be more effective than the dosage and duration of therapy which we employed. Serial cultures and studies of sensitivity are a prerequisite in the selection of cases for streptomycin therapy.

It is not our intent to recommend parenteral or local administration of streptomycin and penicillin in lieu of the sound principles of surgical intervention in the treatment of this conditon. From what we have learned, it seems that both the possibilities and the limitations are far reaching. The intelligent use of antibiotics also shows promise in the treatment of fresh compound fractures. Again the principles of débridement, asepsis and immobilization are cardinal, but the parenteral use alone of penicillin and streptomycin appears logical, since there is usually an adequate blood supply to a freshly traumatized region. On this basis, topical use of antibiotics for fresh fractures, otherwise adequately treated, would seem superfluous. Additionally, topical application in the case of a fresh fracture could be employed only at the expense of poor or no immobilization.

When we regard our own work critically, certain deficiencies are apparent to us. To say that we have demonstrated an effect is not enough. The ultimate goal in evaluating a drug lies in the determination of the optimal conditions under which it may be given to produce a maximal effect. On the assumption that much can be learned from analysis of the shortcomings of such a study, some pertinent considerations are in order.

In the majority of cases of chronic traumatic osteomyelitis of two and three years' duration, penicillin was used early. During the course of treatment, sometimes following operation, penicillin was again administered. Perhaps the patients have received several courses of penicillin. There may have been early elimination of penicillin-sensitive organisms, and then again there may have developed a resistance of the organisms to penicillin, despite the fact that drug fastness is less frequently observed with this compound.[19] Is penicillin now a useful drug in the treatment of such an infection? In the event of an acute exacerbation of the osteomyelitis, to what extent is penicillin now effective after multiple courses? It is apparent that only careful quantitative studies of sensitivity can throw some light on this problem.

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In the case of streptomycin resistance, studies of sensitivity indicating exactly where inhibition of growth in a culture medium ends should be made at frequent intervals if the correct duration of therapy and dosage are to be obtained. In our cases, the majority of studies were not carried beyond 50 units per cubic centimeter. From what is known of streptomycin resistance, it is so far presumed that within two weeks a tremendous resistance may be obtained.

In parenterally treated patients who have been without the benefit of surgical intervention for a long time, serial studies of sensitivity at frequent intervals indicating the minimum amount of streptomycin necessary to inhibit all growth in culture mediums are of even more importance, since some index of the extent to which the antibiotics are permeating the region of infection is obtained thereby.

SUMMARY

1. Results of stretpomycin therapy in 26 cases of chronic traumatic osteomyelitis and 4 cases of infection following bone grafts have been presented.

2. Intramuscular administration of streptomycin appears to have a role in the treatment of chronic traumatic osteomyelitis. From our studies, it appears that it can best be employed as an adjunct to surgical treatment.

3. In regard to the local administration of streptomycin and penicillin it is recognized that some form of continuous method should be used. Local administration of penicillin and streptomycin is recommended in selected cases of chronic osteomyelitis.

4. If streptomycin and penicillin are to be used in cases of chronic osteomyelitis, the following factors must be taken into account: (*a*) massive fibrosis surrounding the infection, (*b*) development of drug fastness, (*c*) the presence of occult foreign bodies and sequestrums, (*d*) determination of dosage, and (*e*) cultures and studies of sensitivity.

IDENTIFICATION OF THE TOXIN OF CLOSTRIDIUM ORGANISMS IN EXPERIMENTAL INTESTINAL OBSTRUCTION

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FOR MANY years investigators have been endeavoring to solve the problem of the cause of death from intestinal obstruction. The complexity of factors associated with this disease and the present lack of sufficient direct evidence to support any single explanation for morbidity and death have been the principal reasons for the lack of agreement among surgeons as to the importance of basic factors operating during the disease process.

From the voluminous mass of experimental and clinical data which has accumulated, many theories have evolved in an attempt to explain the lethal mechanisms and pathologic alterations occurring during the course of the disease. The present status of these many hypotheses has been carefully evaluated recently by Wangensteen,[1] Knight and Slome,[2] Donalson [3] and Besser [4] and need not be reviewed in this paper.

The majority of recent experimental work on intestinal obstruction has placed the emphasis on the factors of electrolytic imbalance and hemodynamic dysequilibrium. The older concept of a toxemia or autointoxication principle has been relegated to a place of secondary consideration. The basic work of Murphy and Brooks,[5] Dragstedt and his associates,[6] Davis and Stone,[7] and Williams [8] and, in recent years,

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From the Department of Surgery, Northwestern University Medical School.

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Sarnoff and others,[9] Blain and Kennedy,[10] Laufman [11] and Davis and his associates [12] cannot be overlooked, however, and may be considered as substantial evidence that a bacterial toxin plays a definite role in the production of the morbid state of intestinal obstruction.

The chief objection to the theory that a toxic substance helps initiate many of the physiologic alterations present in this disease is based on the fact that the direct identification of a specific, lethal toxin, or its mode of absorption from the obstructed intestine, has never been accomplished. Histamine,[13] nucleoprotein,[14] heteroproteose,[15] and choline and neurine [16] have been identified in filtrates of obstructed intestine, but these factors cannot be held primarily responsible for death. Their depressor action, nevertheless, may certainly play a role in the production of the shocklike state seen in dying animals.

Results obtained from recent studies on experimental appendicitis have indicated that the toxemia present in this disease results from the absorption of the toxin of clostridium organisms into the general circulation. We have been able to identify directly the toxin of the clostridium organisms from the gangrenous exudate resulting from experimentally produced appendical peritonitis.[17] This direct titration is dependent on the enzymatic action of the alpha toxin of the organisms. In 1941 MacFarlane [18] demonstrated that the enzyme lecithinase was the lethal component of the type A Clostridium welchii toxin and was probably identical with the specific alpha toxin fraction. She also pointed out that this enzyme will hydrolyze the lecithin in a dilute egg yolk solution, with a resulting production of turbidity. This phenomenon was also studied by Van Heyningen [19] and later by McClean,[20] and a technic for the direct identification and estimation of the clostridium toxin was developed.

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Our present study has been undertaken in an effort to identify the clostridium toxin from the lumen of strangulated small intestine in the dog. Samples of abdominal exudate, present with such an obstruction, were also analyzed for the enzyme. Antitoxic properties of the serum of dogs which had recovered from experimental appendical peritonitis were studied in order to substantiate our earlier concept that commercially prepared polyvalent gas gangrene antitoxin does not inhibit the enzymatic action of clostridium toxin in the dog with the same specificity as does serum obtained from convalescent experimental animals.

EXPERIMENTAL METHODS

Random, healthy, mongrel dogs were used in the experiment. The dogs were fasted for twenty-four hours and then given morphine and atropine intra-

TABLE 1.—*Spectrophotometric Analysis of Turbidity Produced by Lecithinase Present in Intestinal Obstruction in the Dog*

Dog	Length of Strangulated Loop, Cm.	Period After Which Reoperation Was Performed, Hr.	Percentage of Transmission	
			Contents of Strangulated Bowel, Percentage	Abdominal Exudate, Percentage
1	25	24	42	Negative
2	25	24	65	76
3	25	23	61	87
4	25	17½	37	65
5	35	5	27	Negative
6	35	5½	33	Negative
7	35	17¼	43	Negative
8	35	17½	32	75
9	35	17½	Negative	Negative
10	35	17½	41	Negative
11	35	3¾	Negative	Negative
12	35	3	Negative	Negative
13	35	18	80	Negative
14	35	18	59	Negative

muscularly, followed in thirty minutes by pentobarbital (sodium nembutal®) intravenously. The dog's abdomen was shaved clean and painted with 1 per cent iodine followed by 70 per cent alcohol. A 3 inch (7.6 cm.) right rectus incision was made and the terminal portion of the ileum identified and brought up into the wound. Fifteen centimeters from the ileocolic junction a loop of small intestine was isolated and a heavy cotton ligature was placed about its base. The exact length of this loop varied in the series (table 1). The heavy cotton ligature was then carefully tightened until arterial pulsations in the mesenteric vessels were barely palpable. In this way a closed intestinal loop with complete venous and partial arterial strangulation was produced (fig. 1 *A*).

The abdominal wall was closed in three layers with the use of fine black silk sutures, and the dogs were returned to their cages. No supportive therapy of any kind was given to the animals.

Strict aseptic technic was carried out during the procedure except that rubber gloves were not worn by the surgeon.

At various intervals after this procedure (table 1) the dogs were again anesthesized and the abdominal cavity reopened. In several instances the animals died while being given the second anesthetic or while preparations for the operation were being made. These were immediately opened and the strangulated intestine and abdominal exudate removed. All animals found dead in their cages were discarded from the series.

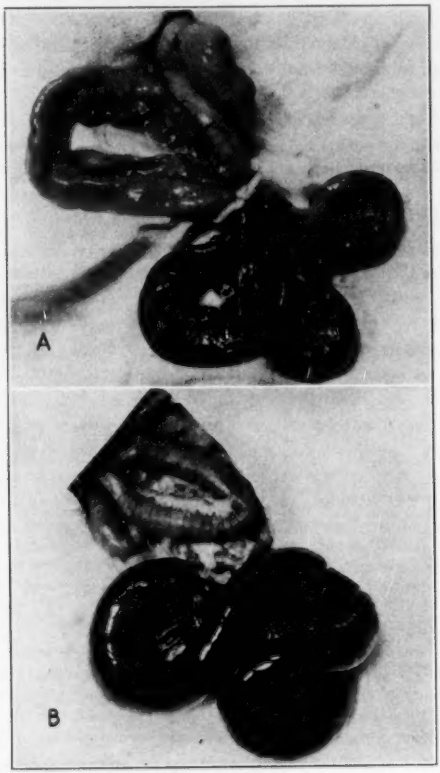

Fig. 1.—*A*, method used in producing experimental low ileal strangulation obstruction in the dog. The loop of small intestine is 35 cm. long and has been taken 15 cm. from the ileocolic junction. *B*, the same strangulated obstructed loop of ileum as shown in *A*, eighteen hours later. The bowel is black and dilated but gross perforation has not occurred. The abdominal viscera show no evidence of bacterial peritonitis.

At the second procedure the strangulated segment of small intestine was found to be black and dilated with a thick, hemolytic, foul-smelling material. The wall of the bowel was thin and friable. The abdominal cavity contained up to 200 cc. of a thin, darkly hemolytic fluid (fig. 1 *B*).

In some animals the wall of the distended segment of intestine had ruptured and allowed the intraluminal contents to pour out into the abdominal cavity. These were discarded from the series. Only those in which the wall was grossly intact at the time of the second procedure were used in the study.

Forty to 50 cc. of the abdominal exudate was removed from the abdominal cavity and placed in a sterile flask. The segment of unruptured strangulated intestine was then removed and placed in a second container and opened. A volume of isotonic sodium chloride solution equal to from 30 to 40 per cent of the contents was added in order to make the material thin enough to be processed.

The fluids were then placed in conical tubes and centrifuged at 1,500 revolutions per minute for ten minutes to remove most of the particulate matter. The supernatant fluid was passed through a Seitz filter, and the clear, dark red fluid was used in our investigation.

Determinations of lecithinase were carried out according to the technic described by McClean [20] except that 0.5 cc. samples of the exudate were analyzed. This procedure is based on the ability of lecithinase to hydrolyze the lecithin present in a dilute egg yolk solution with the production of turbidity and is a very sensitive test.

Earlier work by us had indicated that the commercially prepared polyvalent gas gangrene antitoxin had less specific inhibitory action against the lecithinase activity of the clostridium organisms in the dog than did the serum of dogs convalescing from gangrenous, intraperitoneal lesions. Therefore, two controls were set up for each analysis. One contained commercial polyvalent gas gangrene antitoxin (Lederle). The second contained serum of a dog which had recovered from experimental appendical peritonitis. All turbidimetric analyses were done on a Coleman Universal Spectrophotometer. Readings were recorded as percentage of transmission in the tube containing the fluid sample as compared with an arbitrary 100 per cent transmission set for the tube containing the fluid sample plus serum taken from a convalescent dog.

RESULTS

Twenty animals were used in the experiment. Six of these died before the gangrenous bowel and exudate could be removed and were, therefore, discarded from the series.

The shortest period after which the strangulated intestine and exudate were removed was three hours. Lecithinase could not be identified in the animal, although the bowel appeared black and dilated. Another dog was reoperated on at three hours and forty-five minutes, but toxin could not be identified.

A positive identification of lecithinase from the intraluminal contents of strangulated ileum was first made five hours after the strangulation had been produced. Twelve animals were reoperated on in the period between five and twenty-four hours after strangulation. Lecithinase was identified in the lumen of the obstructed intestine in 11 (91.7 per cent) of these animals (table 1).

Consistent turbidity readings, according to the hour at which the bowel was removed, were not evident in the spectrophotometric determinations. Hydrolysis of the lecithin required an average of ninety

minutes, although complete turibidity was manifested in twenty minutes in the tubes containing material taken five hours and five hours and thirty minutes after strangulation.

Exudate taken from the abdominal cavity, when gross perforation of the strangulated intestinal segment had not occurred, was studied in 12 animals between five and twenty-four hours after strangulation. In only four instances (33.3 per cent) did the enzyme appear in this material. Three of these animals were alive, but extremely lethargic, at the time the material was removed. The remaining animal died while preparation for the second procedure was being made. This animal was autopsied immediately and the material removed.

The inhibition of lecithinase activity of the gangrenous bowel content by serum taken from dogs which had recovered from experimental appendical peritonitis was studied in 12 animals (table 2). In each of

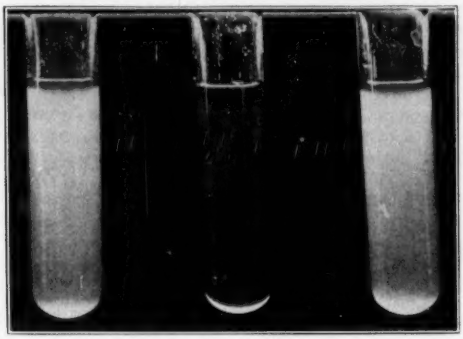

Fig. 2.—Turbidity produced by the hydrolysis of a dilute egg yolk solution by lecithinase present in the contents of obstructed ileum in the dog. The tube on the left contains 0.5 cc. of the processed intestinal contents. Turbidity in this tube identifies the presence of lecithinase (spectrophotometric reading, 41 per cent transmission). The center tube contains 0.5 cc. of the same intestinal contents plus 1.0 cc. of convalescent dog serum. Absence of turbidity in this tube indicates that the neutralization of the lecithinase by this serum has taken place (spectrophotometric reading set at 100 per cent transmission). The tube on the right contains 0.5 cc. of the same intestinal contents plus 1.0 cc. of polyvalent gas gangrene antitoxin. Turbidity in this tube indicates that the commercial antitoxin does not inhibit the lecithinase reaction (spectrophotometric reading, 20 per cent transmission).

these twelve instances comparative analyses using commercial polyvalent gas gangrene antitoxin (Lederle) were carried out. In every case the convalescent serum inhibited the reaction to a greater extent than the commercial antitoxin (fig. 2). In nine of the fifteen determinations which were done, greater turbidity was produced in the tube containing bowel exudate plus commercial antitoxin than in the tube containing bowel exudate alone.

TABLE 2.—*Spectrophotometric Analysis of Turbidity Produced by Lecithinase When Titrated Against Commercial Polyvalent Gas Gangrene Antitoxin and Convalescent Dog Serum*

Dog	Percentage of Transmission: Contents of Strangulated Intestine Alone, Percentage	Contents of Strangulated Intestine Plus Dog Serum,* Percentage	Contents of Strangulated Intestine Plus Commercial Antitoxin, Percentage
1	42	100	50
2	65	100	80
3	61	100	29
4	37	100	18
5	27	100	66
6	33	100	27
7	43	100	19
8	32	100	18
10	41	100	20
13	80	100	105
14	59	100	84

Dog	Percentage of Transmission: Abdominal Exudate Alone, Percentage	Abdominal Exudate Plus Dog Serum,* Percentage	Abdominal Exudate Plus Commercial Antitoxin, Percentage
2	76	100	85
3	87	100	80
4	65	100	36
5	75	100	66

*This is an arbitrary setting of the spectrophotometer in order to make comparative transmission readings.

TABLE 3.—*Spectrophotometric Analysis of Control Reactions*

A—Analysis of Extracts of Normal Ileum Taken from the Living Dogs

Dog	Percentage of Transmission: Extract Alone, Percentage	Extract Plus Dog Serum,* Percentage	Extract Plus Commercial Antitoxin, Percentage
1	105	100	96
2	96	100	95
3	96	100	96

B—Analysis of Commercial Polyvalent Gas Gangrene Antitoxin

Sample	Percentage of Transmission: Egg Yolk Solution Alone,* Percentage	Egg Yolk Solution Plus Commercial Antitoxin, Percentage
A	100	98
B	100	100
C	100	105

C—Inhibition of Standard Clostridium Welchii Toxin by Convalescent Dog Serum

Toxin Sample	Minimum Lethal Dose, Amount	Percentage of Transmission: Toxin Alone, Percentage	Toxin-Antitoxin,* Percentage	Toxin-Dog Serum, Percentage
1	2.4 (Pigeon)	29	100	100
2	4.8 (Pigeon)	22	100	92
3	7.2 (Pigeon)	21	100	89

* This is an arbitrary setting of the spectrophotometer in order to make comparative transmission readings.

Control studies were undertaken on three separate samples of commercial antitoxin in order to determine whether this material alone was responsible for turbidity production. All three analyses gave negative results (table 3).

A 35 cm. loop of the terminal portion of the ileum was resected from 3 normal dogs and processed in the same manner as the strangulated intestinal loops. Lecithinase activity was negative in all three extracts (table 3).

Antitoxin properties of convalescent dog serum against standard Cl. welchii toxin (Eli Lilly) was determined in three titrations (fig. 3). The dog serum inhibited the commercial toxin to a significant degree in every instance (table 3).

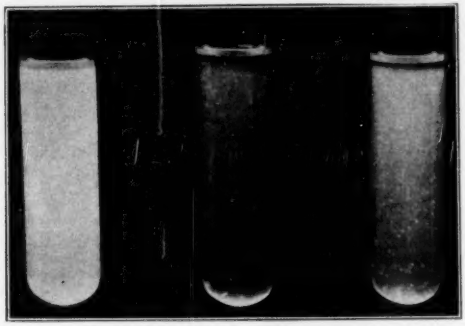

Fig. 3.—Neutralization of standard Clostridium welchii toxin by convalescent dog serum. The tube on the left contains 7.2 minimum lethal dose (pigeon) of Cl. welchii toxin. Turbidity in this tube produced a spectrophotometric reading of 21 per cent transmission. The center tube contains 7.2 minimum lethal dose (pigeon) of Cl. welchii toxin plus 1.0 cc. of polyvalent gas gangrene antitoxin. Absence of turbidity in this tube indicates neutralization of the toxin by the antitoxin. Spectrophotometric reading was set at 100 per cent transmission. The tube on the right contains 7.2 minimum lethal dose (pigeon) of Cl. welchii toxin plus 1.0 cc. of convalescent dog serum. Spectrophotometric reading of 89 per cent transmission indicates that this serum inhibits a standard Clostridium welchii toxin to a significant degree.

COMMENT

The present lack of agreement among surgeons and research workers regarding the importance of morbid factors associated with intestinal obstruction indicates that the basic pathologic mechanisms occurring during the course of the disease are still not clearly understood. In spite of this, however, the experimental work which has been undertaken in an effort to solve the problem has served as a sound basis for the development of rational supportive therapy. The tremendous decrease in deaths

due to intestinal obstruction in recent years serves as dramatic evidence of the importance of these adjunctive measures.

It does not seem probable that any single factor can be held entirely responsible for death from obstructions of the intestinal tract. It is more logical to assume that several elements play a part in the production of the lethal process. A better understanding of electrolytic imbalance and fluid loss has greatly advanced the knowledge of morbid mechanisms; but until further specific identification of toxic products from obstructed intestine has been accomplished and their lethality, mode of action and route of absorption proved and evaluated, the answer to the problem of morbidity and death from intestinal obstruction will be largely a matter of conjecture.

The demonstration of the enzymatic properties of the toxins of the clostridium organisms has permitted their direct identification by means of chemical and spectrophotometric methods. Application of these methods to the analysis of the intestinal contents and abdominal exudate in dogs suffering from low ileal strangulation obstruction has enabled us to identify the toxins of the clostridium organisms in significant amount in 91.7 per cent of the animals studied. The specific identification of such a lethal toxin from the intraluminal contents of strangulated obstructed intestine would certainly qualify the possibility that this factor could help initiate many of the pathologic alterations observed in moribund animals. The early appearance of the toxin and the relatively higher activity at this earlier period are compatible with the growth curve and toxin production of clostridium organisms when a suitable medium for growth is provided.[18]

Identification of the toxin from abdominal exudate when gross perforation of the obstructed bowel has not occurred would indicate that the toxin is able to transverse the wall of the bowel before any demonstrable necrosis has occurred. It is certainly justifiable, however, to assume that the purely mechanistic factors of intraenteric pressure would hasten the process of gangrene. But when rupture does occur and the peritoneal cavity is flooded with intraluminal contents containing high titers of lethal toxins, death probably ensues very rapidly. That bacterial peritonitis can be held responsible for death in few experimental animals subjected to intestinal obstruction is evidence that death due to absorption of toxins occurs before peritonitis can develop.

In 1 of the 4 dogs from which lecithinase was identified in the abdominal exudate when a gross perforation of the strangulated segment had not occurred the material was removed at the moment of death. The remaining 3 animals were living at the time the material was removed. How close to rupture the bowel was at that time or how much longer the animals would have survived cannot be stated. However, our inability to detect the enzyme in the majority of abdominal fluids

would point to the fact that the animals in which the toxin was detected in the fluid were killed close to the point when rupture, or death, would have occurred—a point at which a measurable amount of toxin had already passed through the intestinal wall.

The irreversible changes produced by the lecithinase activity of the clostridium toxin on the lipoprotein components of the host's tissues, especially in the cell membrane and intracellular substratum, must certainly enhance the effect of other factors operating in the morbid process. The enzymatic properties of this toxin are not the single cause of death, but the disintegration of the basic cellular elements whose integrity is dependent on the presence of lecithin probably plays a vital part in producing morbidity and death.

The antienzymatic properties of the serum from convalescent dogs have been demonstrated in every titration carried out in this experiment. The serum used was taken from dogs which had recovered from experimental appendicitis and is undoubtedly a polyvalent antitoxin for many organisms beside the clostridia. The specificity of the lecithinase reaction, however, has been clearly demonstrated and it must, therefore, be assumed that the inhibition of the reaction by this serum is dependent on its neutralization of the clostridium toxin. This concept is substantiated by the fact that convalescent dog serum inhibits the activity of a commercially prepared, standardized Cl. welchii toxin (Eli Lilly) to a significant degree (table 3).

Several species of the clostridium group of organisms have demonstrated their ability to produce lecithinase, among them being Cl. welchii, Clostridium oedematiens, Clostridium hemolyticum and the Clostridium sordelli-Clostridium bifermentans group.[21] An attempt to specifically identify the species responsible for the enzyme production in strangulated intestinal obstruction in the dog has not been undertaken.

A satisfactory explanation for the greater degree of turbidity recorded in the reaction involving the bowel extract plus commercial polyvalent gas gangrene antitoxin than in the reaction involving the bowel extract alone cannot be given at this time. Control studies on three separate samples of this antitoxin have given no indication that the antitoxin itself is involved.

It must be emphasized that the direct, in vitro identification of the toxin of the clostridia from the products of strangulated, obstructed intestine is merely another step toward the ultimate solution to the problem of morbidity and death from this disease. Further aggressive investigation is necessary in order to clarify and evaluate the route of absorption, physiologic action and lethal concentration of this enzyme.

21. McClung, L. S., and Toabe, R.: J. Bact. **53**:139, 1947.

It must also be kept in mind that there is still a question of whether organisms of the clostridium group are normally inhabitant in various tissues in the dog. Such a possibility would lead to the assumption that antibodies against clostridium toxin are a normal property of dog serum. This factor must be taken into account when experimental results obtained with the use of the dog as an experimental animal are being evaluated.

SUMMARY AND CONCLUSIONS

Lecithinase, the lethal factor of the toxin of the organisms of the clostridium group, has been directly identified in the contents of the lumen of obstructed, strangulated small intestine in the dog in 91.7 per cent of the animals studied. This toxin has been identified in the abdominal exudate present with such an obstruction in 33.3 per cent of the cases when gross perforation of the obstructed segment has not occurred.

The inability of commercial polyvalent gas gangrene antitoxin to inhibit the hydrolysis of lecithin by the toxin of the clostridia harbored in the dog has been demonstrated.

Serum taken from dogs which have recovered from gangrenous intraperitoneal lesions will prevent the hydrolysis of lecithin by the lecithinase identified in obstructed, strangulated small intestine in the dog. This convalescent serum will also inhibit the hydrolysis of lecithin by standard Cl. welchii toxin.

TUBULATION OF THE URINARY BLADDER IN REPAIR OF LOW URETERAL INJURIES

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ONE OF the major hazards in radical pelvic surgery for malignant disease is injury to the ureters. The purpose of this report is to describe a method of repair of the ureter when the site of injury is in the lower segment, i. e., that portion lying within the parametria.

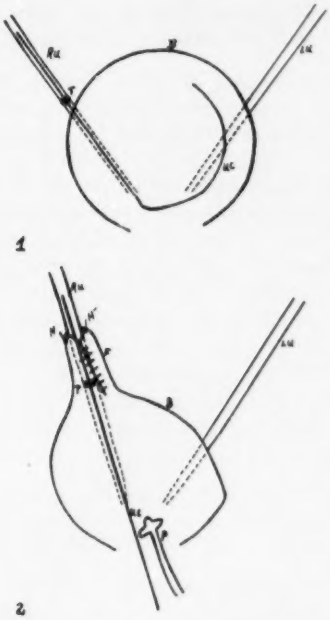
If the transection is complete, a no. 7 or 8 (French) ureteral catheter is inserted upward in the upper segment and the lower end of the catheter is then placed into the lower segment and pushed into the bladder. The whole catheter is then threaded downward, coiling in the bladder until the upper tip is about 8 to 10 cm. above the site of injury. The transected ureter is repaired over the catheter, four or five interrupted 00000 surgical gut sutures with an atraumatic needle being used. The posterior-superior portion of the bladder is grasped with Allis clamps and pulled upward on the lateral aspect of the repaired ureter and is anchored to the fold of mesentery (or ureteral tissue) at a point about 4 to 6 cm. above the site of injury, 2 or 3 interrupted sutures of surgical gut (size 0) or silk being used (figure, *1*). With the same type of suture material the stretched up portion of the bladder is then tubulated about the ureter in such a fashion as to enclose the lower 6 to 8 cm. of the ureter completely. A single row of interrupted sutures about three quarters of a centimeter apart suffices. A soft rubber drain is placed in the vicinity of the repair and the abdominal wound closed.

The ureteral catheter is then brought out from the bladder through the urethra, secured by adhesive tape to the inner aspect of the thigh and connected to rubber tubing which leads into a bottle separate from that into which the retention catheter, which is also placed into the bladder, drains. The ureteral catheter remains in situ for fourteen to eighteen days. In one instance it was accidentally pulled out on the ninth day and no complications ensued.

From the Memorial Hospital for the Treatment of Cancer and Allied Diseases.

When transection of the ureter is incomplete (50 per cent), the ureteral catheter is threaded into the ureter in the same fashion as that described previously, through the opening in the ureter. Of course, care is exercised to prevent further tearing of the ureter with complete division of it.

This method of repair has been employed in 6 patients. These underwent radical panhysterectomy with excision of pelvic lymph nodes



1, schematic diagram of tubulation of urinary bladder about divided ureter. *B* indicates bladder, *RU* and *LU* right and left side of ureter respectively, *T* site of end to end anastomosis of divided ureter and *UC* ureteral catheter in right side of ureter with lower end coiled in bladder. *2*, diagram after tubulation of bladder about site of repaired injury in right side of ureter. The right portion of the bladder has been drawn up and sutured a few centimeters above *T*, the anastomosed ureter. *H'* and *H'*, indicate sutures anchoring upper portion of tubulated bladder to surrounding mesentery or periareolar tissue. The site of the ureteral anastomosis is well within the tubulated bladder. The ureteral catheter has been drawn out of the urethra, and the Pezzer catheter, *P*, has also been placed in the urethra to drain the bladder of urine coming from the left side of the ureter.

for recurrent and advanced carcinoma of the uterus with direct spread into parametria (periureteral tissues). In 4 complete division of the ureter occurred, and in 2 about three quarters of the ureter was divided.

Among the 4 patients, the division of the ureter was purely accidental in 3 cases and in the fourth case a segment 1 cm. in length was intentionally removed to circumvent secondary invasion by neoplastic disease. Healing was complete, there being no fistulas in any of the 4 instances described and no instance of subsequent pyelonephritis or cystitis.

The principle underlying the method of repair is that the site of injury is deeply placed within peritoneum-covered surfaces (those of the bladder) and thus a maximal opportunity for "sealing" is afforded. The displacement and distortion of part of the urinary bladder incident to the procedure are such as to cause no disturbance of function.

HETEROTOPIC PANCREATIC TISSUE AND GASTRIC MUCOSA IN MECKEL'S DIVERTICULUM

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AND
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ONE OF the more common developmental abnormalities of the intestinal tract is Meckel's diverticulum. Although probably recognized and described as early as 1598 by Hildanus, it was not until 1809 that Johann Frederic Meckel [1] clarified the origin and significance of this diverticulum. Developmentally, it is formed by the persistence of the proximal or intestinal end of the vitelline duct which connects the yoke sac with the midgut.

The incidence of Meckel's diverticulum is from 1 to 2 per cent as shown by Christie [2] and Harkins,[3] who reviewed some 30,000 autopsies. That the diverticulum is relatively common can be attested to by nearly every surgeon who has had some experience with the various complications associated with this embryologic abnormality.

Heterotopic tissue in Meckel's diverticulum is not uncommon, being present in 15 to 25 per cent of all diverticula.[4] The incidence of heterotopic tissue rises to 60 to 75 per cent of cases of Meckel's diver-

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From the Department of Surgery of the University of Chicago.

The engravings used to illustrate this article were made possible by grants from the Douglas Smith Foundation for Medical Research of the University of Chicago.

1. Meckel, J. F.: Ueber die Divertikel am Darmkanal, Arch. f. d. ges. Physiol. **9**:421, 1809.

2. Christie, A.: Meckel's Diverticulum. A Pathologic Study of Sixty-Three Cases, Am. J. Dis. Child. **42**:544 (Sept.) 1931.

3. Harkins, H. N.: Intussusception due to Invaginated Meckel's Diverticulum: Report of Two Cases with Study of One Hundred Sixty Cases Collected from Literature, Ann. Surg. **98**:1070, 1933.

4. (*a*) Schaetz, G.: Beiträge zur Morphologie des Meckel'schen Divertikels, Beitrz. path. Anat. u. z. allg. Path. **74**:115, 1925. (*b*) Meckel, J. F.: Handbuch der pathologischen Anatomie, Leipzig, C. H. Reclam, 1812, vol. 1, p. 553. (*c*) Curd, H. H.: A Histologic Study of Meckel's Diverticulum with Special Reference to Heterotopic Tissues, Arch. Surg. **32**:506 (March) 1936 . (*d*) Matt, J. G., and Timpone, P. J.: Peptic Ulcer of Meckel's Diverticulum: Case Report with Review of Literature, Am. J. Surg. **47**:612, 1940.

ticulum causing symptoms.[5] An example is peptic ulceration of heterotopic gastric mucous membrane. The group causing symptoms probably represents only one fourth of all diverticula.

Although gastric mucosa is the most common heterotopic tissue found in Meckel's diverticulum, aberrant pancreas was reported first by Zenker in 1861.[6] Gastric mucosa is followed in incidence by duodenal mucosa, pancreatic tissue, colonic mucosa and various combinations of these tissues.

Pancreatic tissue in Meckel's diverticulum is relatively rare. We have been able to find 30 cases reported in the literature. Excellent reviews of pancreatic heterotopia have been published by Hunt and Bonesteel,[7] Faust and Mudgett [8] and Barbosa, Dockerty and Waugh.[9] The last authors reported that the incidence of aberrant pancreas in Meckel's diverticulum makes up about 5.3 per cent of all cases of pancreatic heterotopia. Hallendorf and Lovelace [5] and Schaetz [4a] reported an incidence, based on relatively small series, of 2 and 2.7 per cent pancreatic heterotopia in Meckel's diverticulum. It is difficult to find any figures in the recent literature covering the incidence of pancreatic heterotopia in Meckel's diverticulum. This is probably due to the small number of cases in the series reviewed. Consequently the percentages quoted are not of much value.

Hunt and Bonesteel [7] reviewed an additional series of 8 cases (1870 to 1909) of diverticulum of the terminal portion of the ileum containing aberrant pancreas. Siegmund [10] and Barbosa, Dockerty and Waugh [9] reported similar cases. These may be cases of true Meckel's diverticulum but were not designated as such by the authors. In 1 case, that of Nauwerck,[11] a true Meckel diverticulum was found in addition to the more proximal diverticulum containing pancreatic tissue.

With the small number of cases of Meckel's diverticulum containing aberrant pancreas, one would expect the incidence of Meckel's diver-

5. Hallendorf, L. C., and Lovelace, W. R.: Aberrant Gastric Mucosa and Pancreatic Tissue in a Bleeding Meckel's Diverticulum: Report of a Case, Proc. Staff Meet., Mayo Clin. **22**:53, 1947.

6. Zenker, F. A.: Neben Pancreas in der Darmwand, Virchows Arch. f. path. Anat. **21**:369, 1861.

7. Hunt, V. C., and Bonesteel, H. T. S.: Meckel's Diverticulum Containing Aberrant Pancreas, Arch. Surg. **28**:425 (March) 1934.

8. Faust, D. B., and Mudgett, C. S.: Aberrant Pancreas with Review of the Literature and Report of a Case, Ann. Int. Med. **14**:717, 1940.

9. Barbosa, J. de C.; Dockerty, M. B., and Waugh, J. M.: Pancreatic Heterotopia, Surg., Gynec. & Obst. **82**:527, 1946.

10. Siegmund, H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen Pathologie und Histologie, 1930, vol. 4, no. 3, p. 199.

11. Nauwerck, C.: Ein Nebenpankreas, Beitr. z. path. Anat. u. z. allg. Path. **12**:29, 1892.

ticulum containing both heterotopic gastric and pancreatic tissue to be even less. Schaetz [4a] is credited with reporting the first case in 1925, and he also listed this combination as occurring in 5.4 per cent of the 37 cases of Meckel's diverticulum which he reported. Since then, 6 additional cases have been reported.[12]

At the University of Chicago Clinics one of us (D. C.) recently removed a Meckel diverticulum which contained gastric and pancreatic

TABLE 1.—*Cases of Pancreatic Heterotopia in Proved Meckel's Diverticulum*

1.	Zenker [6]	1861
2.	Schirmer, A. M.: Beitrag zur Geschichte und Anatomie des Pankreas, Inaug. Diseert., Basel, L., Reinhardt, 1893, p. 68	1893
3.	Albrecht, E.: München. med. Wehnschr. **48**: 2061, 1901	1901
4.	Merkel, H.: Sitzungsberichte **19**: (Dec.) 1904	1905
5.	Hedinger: Cor.-Bl. f. Schweiz-Aerzte **36**: 305, 1906	1906
6.	Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, ed. 6 Berlin, G. Reimer, 1911, vol. 1, p. 641	1907
7.	Clogg [13]	1908
8.	Nazari, A.: Bull. d. r. Acad. med. di Roma **35**: 245, 1909	1909
9.	Albrecht and Arzt [14]	1910
10.	Koch, M., and Suguki, T.: Centralbl. f. allg. Path. u. path. Anat. **23**: 904, 1912	1912
11.	Koch, M., and Suguki, T.: Centralbl. f. allg. Path. u. path. Anat. **23**: 904, 1912	1912
12.	Schaetz [4a]	1925
13.	Cogniauz [15]	1928
14.	Hunt and Bonesteel [7]	1934
15.	Branch and Gross [12c]	1935
16.	Branch and Gross [12c]	1935
17.	Branch and Gross [12c]	1935
18.	Branch and Gross [12c]	1935
19.	Branch and Gross [12c]	1935
20.	Branch and Gross [12c]	1935
21.	Hill and Cohen [12d]	1937
22.	Black and Packard [12a]	1938
23.	Derbyshire, R. C.: Studies of Accessory Pancreas, Thesis, University of Minnesota Graduate School, 1940	1940
24.	Morison, J. E.: Brit. J. Surg. **29**: 139 (July) 1941	1941
25.	Troll [12b]	1944
26.	Troll [12b]	1944
27.	Barbosa, Dockerty and Waugh [9]	1946
28.	Barbosa, Dockerty and Waugh [9]	1946
29.	Hallendorf and Lovelace [5]	1947
30.	Horsley [12e]	1947
31.	Bigelow and Clark	1948

tissue. Search of the literature established its rarity, and we are reporting it as the thirty-first case of aberrant pancreas (table 1) and the

12. (*a*) Black, W. C., and Packard, G. B.: Surgical Complications Resulting from Presence of Heterotopic Tissue (from Gastric Mucosa and Pancreas) in Meckel's Diverticulum, Rocky Mountain M. J. **35**:859, 1938. (*b*) Troll, M. M.: Aberrant Pancreatic and Gastric Tissue in the Intestinal Tract, Arch. Path. **38**:375 (Dec.) 1944. (*c*) Branch, C. D. and Gross, R. E.: Aberrant Pancreatic Tissue in the Gastrointestinal Tract, Arch. Surg. **31**:200 (Aug.) 1935. (*d*) Hill, F. C., and Cohen, L.: Meckel's Diverticulum Containing Aberrant Gastric Mucous and Pancreatic Tissue, Nebraska M. J. **22**:187, 1937. (*e*) Horsley, J. S., and Keasbey, L. E.: Tumors of the Small Intestine, in Lewis, D.: Practice of Surgery, 1947, vol. 6, chap. 17, p. 34. (*f*) Hallendorf and Lovelace.[5]

eighth case of combined pancreatic and gastric heterotopia in a proved case of Meckel's diverticulum (table 2).

TABLE 2.—*Cases of Both Pancreatic and Gastric Heterotopia in Proved Meckel's Diverticulum*

1.	Schaetz [4a]	1925
2.	Branch and Gross [12c]	1935
3.	Hill and Cohen [12d]	1937
4.	Black and Packard [12a]	1938
5.	Troll [12b]	1944
6.	Hallendorf and Lovelace [5]	1947
7.	Horsley [12e]	1947
8.	Bigelow and Clark	1948

REPORT OF A CASE

M. B., a 14 year old school girl, had no history of gastrointestinal complaints prior to the onset of generalized abdominal pain. Some hours later this pain radiated to the right lower quadrant and increased in severity. Examination of the abdomen revealed marked rigidity and spasm in the right lower quadrant, with rebound tenderness referred to McBurney's point. A white blood cell count was 18,800, with a notable shift to the left.

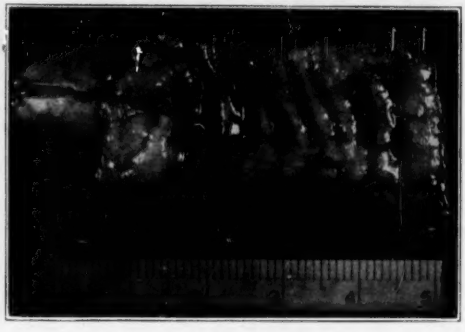

Fig. 1.—Photograph of opened Meckel's diverticulum showing nodule of pancreatic tissue at the tip, hypertrophic fold of gastric mucosa and circular folds of ileal mucosa.

Abdominal exploration confirmed the diagnosis of acute appendicitis, and an appendectomy was performed. In addition a Meckel diverticulum with a nodule of firm yellow tissue at the tip was removed from the terminal portion of the ileum about 45 cm. from the ileocecal valve. The patient's convalescence was uneventful.

The Meckel diverticulum was 5.5 cm. long and 2.5 cm. in circumference. The distal 1.5 cm. was delimited from the rest by a groove. This nodule of firm yellow tissue was encapsulated and resembled pancreas. When the diverticulum was opened its mucosa had the transverse folds resembling small bowel mucosa

except for several polypoid folds at the tip (up to 1 cm. in thickness). Here the mucosa was pinker and resembled gastric mucosa (fig. 1).

Microscopically the yellow nodule at the tip was pancreatic tissue made up of normal islets, ducts and acini (fig. 2). Parts of the stroma included smooth muscle fibers, probably of the intestinal musculature. The large pancreatic ducts

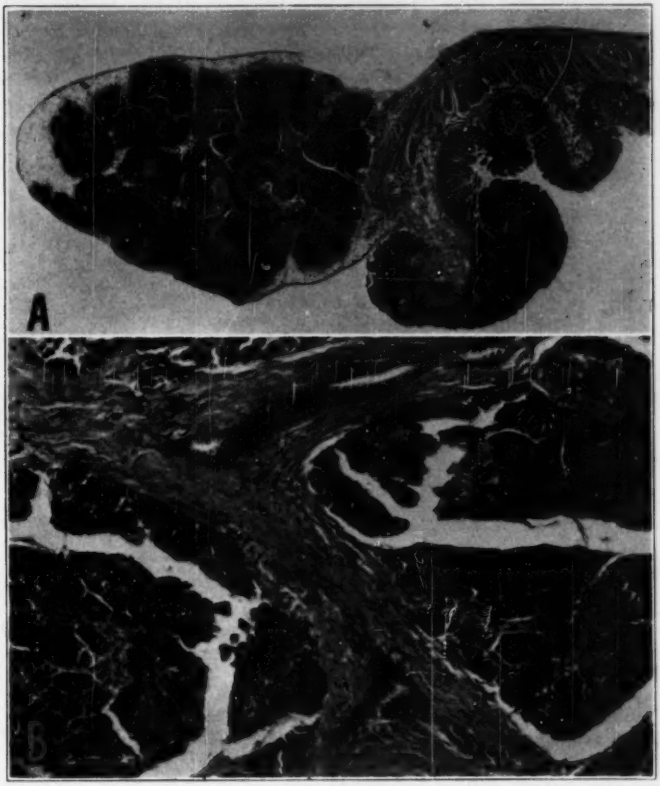

Fig. 2.—*A*, low power photomicrograph (8 ×) of a longitudinal section through the end of the Meckel diverticulum. The nodule of pancreatic tissue, the fold of gastric mucosa and the ileal mucosa are easily recognizable. *B*, high power photomicrograph (250 ×) of the pancreatic tissue at the tip of the Meckel diverticulum showing the acinar tissue, islets of Langerhans and pancreatic ducts.

were not dilated, and this plus the absence of atrophy indicated that the ducts must have opened into the diverticulum. The polypoid folds at the tip were gastric

mucosa containing many acid and peptic cells (fig. 3). The remainder of the diverticulum had the normal coats of the small bowel. There was no gross or microscopic evidence of recent or old ulceration or of inflammation of the mucosa.

COMMENT

The origin of heterotopic pancreatic tissue in Meckel's diverticulum is controversial, and the various theories are well presented in the recent articles of Barbosa, Dockerty and Waugh,[9] Hunt and Bonesteel[7] and Troll.[12b]

Histologically the aberrant pancreas is usually normal in structure and arrangement, with acini frequently containing zymogen granules.

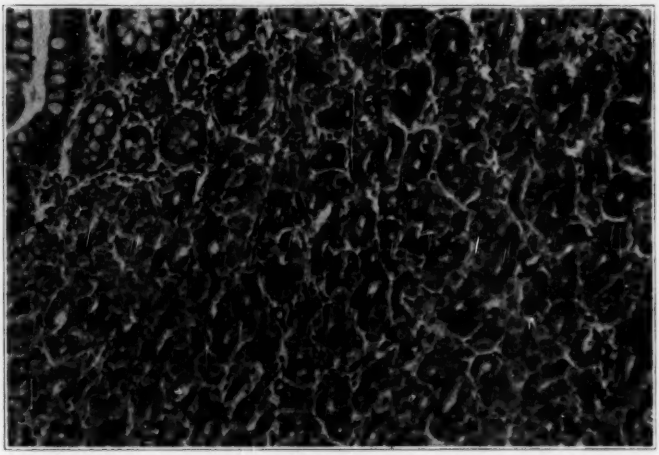

Fig. 3.—A high power photomicrograph (250 ×) of the gastric mucosa contained in the end of the Meckel diverticulum. Both parietal and chief cells are included.

Physiologically it probably functions like normal pancreas. Barbosa, Dockerty and Waugh[9] demonstrated histologic evidence of function in 76 per cent of their cases. Islets of Langerhans may or may not be present. They were present in 39 per cent of their cases.

These nodules of pancreas are usually single and 1 to 4 cm. in diameter, and they are firm, opaque and white or yellow. They rarely lie on the serosal surface, usually being found in the submucosa or infiltrating the muscle fibers. Grossly they often look like pancreas, but they may be mistaken for cancer.

Most of the patients with aberrant pancreas in Meckel's diverticulum were asymptomatic, and the condition was found at autopsy. How-

ever, the diverticulum caused intestinal obstruction in the cases of Clogg [13] and of Albrecht and Arzt [14]; intussusception in the cases of Cogniauz,[15] Troll,[12b] Black and Packard [12a] and Horsley [12c]; hemorrhage from an ulcer in the case of Hallendorf and Lovelace [5]; symptoms simulating appendicitis in the case of Hunt and Bonesteel,[7] and symptoms of biliousness in 1 of the cases of Barbosa, Dockerty and Waugh.[9] Siegmund [10] in 1929 described 3 cases of ileal diverticula containing pancreas which caused invagination. These diverticula were not definitely identified as Meckel's diverticula.

It is interesting to speculate that the presence of alkaline pancreatic secretions in the diverticulum in the case discussed here may have neutralized the acid of the gastric mucosa, thereby preventing ulcer formation with complicating signs and symptoms. The recent case of Hallendorf and Lovelace,[5] with hemorrhage from a Meckel diverticulum containing heterotopic gastric and pancreatic tissue, would tend to disprove this speculation. However, the lack of an accurate histologic description, including presence or absence of ducts, evidence of function of the tissue and the absence of a bleeding point, would invalidate any conclusions from this case.

We feel that any Meckel diverticulum is a potential source of future trouble and should be removed surgically whenever it is possible to do so without appreciable risk.

SUMMARY

1. A case of heterotopic pancreatic and gastric tissue in Meckel's diverticulum is presented. This is the thirty-first case of aberrant pancreas in Meckel's diverticulum and the eighth in which the diverticulum contained both gastric and pancreatic heterotopia.

2. A short discussion of incidence, complications and treatment is included.

13. Clogg, H. S.: Acute Intestinal Obstruction, Lancet **1**:639, 1908.

14. Albrecht, H., and Arzt, L.: Beiträge zur Frage der Gewebsverirrung. II Ueber die Bildung von Darmdivertikeln mit Dystrophischem Pankreas, Frankfurt. Ztschr. f. Path. **4**:167, 1910.

15. Cogniauz, P.: Contribution à l'étude des pancreas aberrants, Arch. franco-belges de chir. **31**:307, 1928.

CHANGES IN COAGULATION TIME ASSOCIATED WITH EXPERIMENTAL ACUTE PANCREATITIS IN DOGS

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AND
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THE PATHOLOGIC anatomy of animals and human beings with acute pancreatitis (pancreatic necrosis) often manifests widespread thromboses, infarctions and hemorrhages, and there is reason to believe that disruption of the blood supply to the parenchyma of the pancreas is necessary for the progression of the lesion from pancreatic edema to pancreatic necrosis.[1] Rich and Duff [2] have shown changes in the medial coat of small arteries within the organ and elsewhere in the body in instances of pancreatitis in man and experimental animals, and they expressed the belief that this damage is specifically due to activated trypsin, a substance which has long been suspected of playing a major role in the dramatic pathologic changes seen in cases of this malady. However, in some classic examples of pancreatic necrosis this vascular lesion has not been demonstrable, which suggests that other factors may be operative in inducing thrombosis and hemorrhage. One of these may be an altered coagulation mechanism, and in view of observed changes in prothrombin time in pancreatitis in man and the known ability of trypsin to act on prothrombin and thrombin, a study of the clotting and prothrombin times of dogs with experimental acute pancreatitis was undertaken.

METHODS

After fasting mongrel dogs weighing between 20 and 30 pounds (9.1 and 13.6 Kg.) had been anesthetized with about 30 mg. per kilogram of pentobarbital sodium, control samples of blood were withdrawn from the external jugular veins.

From the Department of Surgery and the Department of Physiology and Biophysics of the School of Medicine, University of Washington.

1. Popper, H. L.: Acute Pancreatitis: An Evaluation of the Classification, Symptomatology, Diagnosis and Therapy, Am. J. Digest. Dis. **15**:1-4, 1948. Smyth, C. J.: Etiology of Acute Hemorrhagic Pancreatitis with Special Reference to the Vascular Factors: An Analysis of Autopsies and an Experimental Investigation, Arch. Path. **30**:651-669 (Sept.) 1939.

2. Rich, A. R., and Duff, G. L.: Experimental and Pathological Studies on the Pathogenesis of Acute Hemorrhagic Pancreatitis, Johns Hopkins Hosp. Bull. **58**:212-259, 1936.

The abdomen was then entered under aseptic precautions through a high incision, and in a few instances blood was obtained from the portal vein for comparison with specimens from the systemic circulation. The duodenum was elevated and the main pancreatic duct visualized. Usually this was seen before the overlying peritoneum was incised, and it was never necessary to injure the pancreas significantly or interrupt any part of its blood supply. Loops of no. 60 cotton were

TABLE 1.—*Effects of Experimental Pancreatitis on Coagulation, Calcium and Prothrombin Time* *

Dog No.	Time Interval After Injection of Duct	Prothrombin Time, Seconds	Coagulation Time	Calcium Time	Hematocrit Value	Serum Calcium, Mg./100 Cc.	Serum Amylase, Units
2.....	Control	12.5	.....	.....	..	..	...
	30 min.	10.8	.....	.....	..	..	...
	24 hr.	12.7	6'28"	5'12"	..	..	...
3.....	Control	12.7	7' 0"	6'31"	..	..	...
	15 min.	11.3	3'20"	2'45"	..	..	...
	45 min.	11.9	3'20"	3'11"	..	..	...
	1 hr.	11.9	4'47"	3'41"	..	..	...
	4 hr.	11.8	3'58"	2'54"	..	12	...
	24 hr.	12.3	4' 0"	3'41"	36	..	...
	3 days	12.5	6'19"	5'28"	37	..	...
	4 days	12.6	6' 0"	6'19"	44	8	...
	6 days	12.6	6' 7"	8'54"	44	..	...
	7 days	12.9	8'18"	6'27"	40	8.2	...
4.....	Control	13.0	4' 0"	3'54"	..	..	...
	30 min.	10.9	3'10"	2'51"	..	..	...
	2 hr.	11.9	4'39"	4'10"	44	..	...
	48 hr.	13.4	5'27"	4'59"	34	..	...
	3 days	12.4	5'36"	7'15"	36	..	...
	5 days	13.7	6'11"	10'58"	45	11	...
	6 days	13.1	5'54"	5' 4"	25	←———	Vitamin K
5.....	Control	12.0	4'48"	5'47"	..	..	...
	15 min.	10.1	3'18"	5'48"	..	..	...
	20 min.	10.5	3'28"	5'50"	..	..	...
	30 min.	10.4	2'58"	5' 7"	..	..	...
	3 hr.	11.5	4'29"	5'23"	47	..	...
	24 hr.	12.8	6'21"	4'21"	54	9.1	...
	48 hr.	13.3	6'32"	8' 0"	45	..	...
	3 days	13.0	5' 9"	9'15"	40	←———	Vitamin K
	4 days	12.2	5' 7"	5'40"	43	9.2	...
5.....	Control	12.0	4'59"	3'51"	37	..	320
	15 min.	12.1	3'49"	3'12"	45	..	800
	30 min.	10.6	3'20"	2'59"	45	..	1,066
	1 hr.	10.5	2'59"	2'45"	45	..	1,333
	2 hr.	11.6	3' 0"	2'38"	47	..	1,600
	5 days	12.7	4'39"	4'28"	42	..	2,666
	7 days	13.6	6'53"	3'27"	30	..	3,200

* All these animals had acute pancreatitis. Note the striking reductions in prothrombin time and calcium time in dogs 4 and 5 after the injection of vitamin K.

slipped about the duct and the duodenal side ligated. A no. 19 cannula was inserted into the distal lumen, and either 5 to 10 cc. of the animal's own gallbladder bile, previously aspirated by a tangential puncture of the organ with a no. 26 hypodermic needle, or like amounts of a sterile 10 per cent aqueous solution of sodium taurocholate were injected into the duct. The second ligature was tied as the cannula was withdrawn and the duct then divided between the two ties. The gland was observed for a time after the injection to ascertain the effectiveness of the method and then restored to its usual position, and the abdomen was closed in layers with cotton sutures.

No attempt was made to treat the animals. They were covered with blankets until awake, blood samples being withdrawn at the intervals noted in the tables. Standard kennel rations and water were allowed as desired, though the dogs with

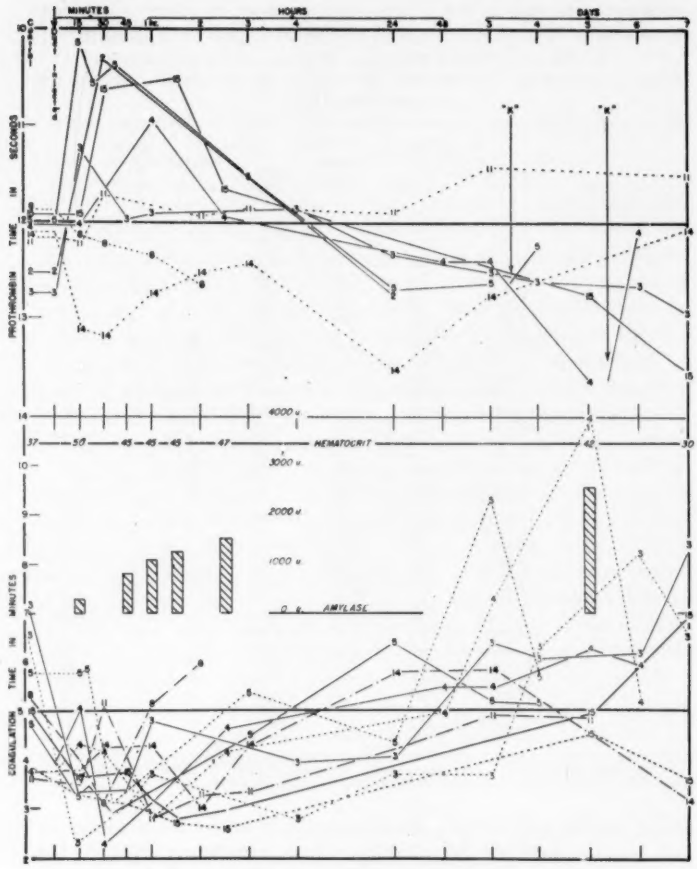

Fig. 1.—Effects of experimental pancreatitis on coagulation, calcium and prothrombin times.

serious pancreatitis vomited and were dehydrated for two or three days. Noticeable steatorrhea or jaundice did not develop in any, and in each instance a complete autopsy was performed to confirm the presence of pancreatitis and exclude the existence of an undiagnosed complicating disease.

Coagulation times were determined by the method of Lee and White,[2] and "calcium time" (Lee and Vincent)[3] was measured simultaneously. Quick's [4] method of prothrombin estimation was used with plasma undiluted and diluted 1 : 1. In most instances a control specimen from one of us was employed as a check and an exact norm of twelve seconds required before proceeding. A method of Somogyi [3] was used to measure the level of serum amylase, and the serum calcium was estimated by Clark's technic.[3]

RESULTS

In 5 dogs either bile or sodium taurocholate solution was injected into the duct. The effects of the resulting pancreatitis on coagulation,

TABLE 2.—*Coagulation, Calcium and Prothrombin Times in Control Animals* *

Dog No.	Time Interval After Operation on Duct	Prothrombin Time, Seconds	Coagulation Time	Calcium Time	Hematocrit Value	Serum Amylase, Units
11	Control	12.1	3'43"	4' 6"	40	360
	15 min.	12.1	3'29"	4'44"	..	400
	30 min.	11.6	5' 8"	6' 9"	..	400
	1 hr.	11.8	2'51"	3' 8"	..	...
	2 hr.	11.8	3'18"	2' 6"	..	...
	3 hr.	11.8	3'20"	2'17"	..	400
	24 hr.	11.8	4'15"	3'20"	43	245
	3 days	11.4	4'52"	3'17"	33	400
	7 days	11.6	4'49"	4'24"	32	457
7	Control	11.0	5'16"	3'55"	..	...
	30 min.	12.7	4' 0"	8'13"	33	...
	90 min.	12.8	7' 0"	6'35"	..	...
	24 hr.	....	5' 0"	6' 1"	..	...
	48 hr.	12.3	6'32"	8' 0"	45	...
	8 days	11.2	3'21"	4'17"	27	...
	19 days	12.1	5' 2"	5'40"	..	...
	35 days	11.9	4'18"	3'13"	29	...
8	Control	11.8	5'26"	3'39"	22	...
	15 min.	12.1	4' 7"	5'15"	..	...
	30 min.	12.2	3'12"	4' 2"	..	...
	1 hr.	12.3	5'10"	4' 9"	..	...
	2 hr.	12.6	6' 0"	5' 2"	30	...
	16 days	11.8	3' 7"	1' 2"	28	...
14	Control	12.0	3'51"	4'19"	24	533
	15 min.	13.0	3'54"	2'54"	..	533
	30 min.	13.0	4'16"	3'31"	..	640
	1 hr.	12.6	4'19"	3'32"	..	640
	2 hr.	12.4	3' 3"	2' 2"	..	800
	3 hr.	12.4	4'26"	3'50"	30	1,066
	24 hr.	13.4	5'52"	4'14"	21	4,000
	3 days	12.7	5'47"	5' 9"	29	2,666
	7 days	12.1	3' 0"	2'21"	32	1,000

* None of these animals had gross evidence of pancreatitis when reexplored or killed.

calcium and prothrombin times were similar in all animals and are presented in table 1 and figure 1. Within fifteen minutes the prothrombin time decreased a second or more, and coincident with this the coagulation and calcium times were reduced. Since the Quick method measures the rate of thrombin formation,[4] the observed change indicates an increased

3. Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis, ed. 3, St. Louis, C. V. Mosby Company, 1943, vol. 1, pp. 514, 522, 288 and 281.

4. Quick, A. J.: The Hemorrhagic Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 35.

speed of conversion of prothrombin to thrombin. A return to the preoperative intervals was reached simultaneously in one or two hours and during the ensuing days the times were significantly and progressively prolonged.

The intravenous injection of 5 cc. of bile or the taurocholate solution into normal fasting dogs was not followed by any consistent change in coagulation, calcium or prothrombin times. Simple exposure and isolation of the duct in fasting animals did not influence the values obtained (dog 11, table 2), nor did double ligation and division of the duct (dogs 7 and 8, table 2) or injection in the pancreatic side with 5 cc. of sterile isotomic sodium chloride solution prior to ligation and section (dog 14, table 2). Though a moderate rise in serum amylase was observed in this last animal none of the control dogs showed gross evidence of pancreatitis when killed.

COMMENT

In 1916 Douglas and Colebrook [5] found that trypsin accelerated the coagulation of blood, and a year later Heard [6] mentioned that the enzyme clotted oxalated blood. In 1935 Eagle proved the effect to be due to trypsin, and then he and Harris [7] showed that certain concentrations of trypsin rapidly converted prothrombin to thrombin. The curve of this power of trypsin reported from their in vitro studies is similar to that seen in our animals with pancreatitis and provides suggestive evidence that activated trypsin is liberated into the circulation in this condition in sufficient concentration to effect the conversion. The possibility that bile or sodium taurocholate might suppress in vivo as chloroform does in vitro the inhibitor which holds in abeyance the tryptase of the albumin fraction [8] seems unlikely inasmuch as no effect on clotting follows the intravenous injection of either of these substances.

Furthermore Eagle and Harris showed that the continued presence of trypsin in proper amounts results in destruction of the thrombin formed even as it continues to effect the change of prothrombin into thrombin. Thus in time the prothrombin is used up. In our dogs with

5. Douglas, S. R., and Colebrook, L.: On the Advantage of Using a Broth Containing Trypsin in Making Blood Cultures, Lancet **2**:180-183, 1916.

6. Heard, W. N.: The Calcium and Phosphorus of the Blood and a Suggestion as to the Nature of the Art of Coagulation, J. Physiol. (London) **51**:294-317, 1917.

7. Eagle, H., and Harris, T. N.: Studies in Blood Coagulation: V. The Coagulation of Blood by Proteolytic Enzymes (Trypsin, Papain), J. Gen. Physiol. **20**:543-560, 1936-1937.

8. Christensen, L. R.: The Activation of Plasminogen by Chloroform, J. Gen. Physiol. **30**:149-157, 1946-1947.

pancreatitis the progressive prolongation of the prothrombin time [9] during the first week after operation suggests that prothrombin is being lost faster than it is being replaced. That this loss is not entirely due to inability of the liver to fabricate prothrombin is shown by the definite decrease in prothrombin time resulting from the subcutaneous injection of 5 mg. of synthetic vitamin K [10] (dogs 4 and 5, table 1).

Since the precursor of the vitamin is fat soluble one might argue that the elimination of pancreatic lipase by occlusion of the main pancreatic duct would be followed by a decline in plasma prothrombin due to lack of absorption of the mother substance. That this does not occur within a week is shown by the records of 2 animals (dogs 7 and 8, table 2) in which the duct was simply ligated and studies continued at intervals for thirty-five and sixteen days respectively; no increase in prothrombin time resulted.

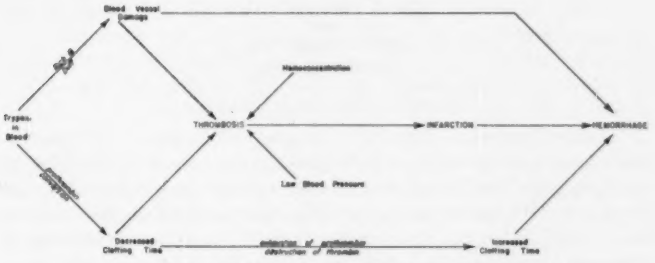

Fig. 2.—Factors influencing bleeding in pancreatitis.

It therefore seems probable that in experimental pancreatitis activated trypsin is released into the general circulation in sufficient quantity to accelerate the conversion of prothrombin to thrombin. Simultaneously the coagulation time is significantly altered. The progressive lengthening of the prothrombin time after the first few hours suggests that the available prothrombin is being depleted, and the coincident prolongation of the clotting time may be another indication of this or may signify destruction of thrombin by the continued action of trypsin.

Figure 2 illustrates the implications of these findings in reference to the pathogenesis of the vascular lesions of acute pancreatic necrosis.

9. A low percentage of prothrombin has been observed by one of us (E. P. L.) in the absence of demonstrable hepatic disease in patients with chronic recurring pancreatitis. In these patients the prothrombin rises temporarily after the injection of synthetic vitamin K.

10. Menadione sodium bisulfite U. S. P. (hykinone®).

PROGRESS IN ORTHOPEDIC SURGERY FOR 1945

A Review Prepared by an Editorial Board of the American Academy of Orthopaedic Surgeons

TUMORS OF BONE AND OF SYNOVIAL MEMBRANE

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BENIGN OSTEOGENIC TUMORS

Osteoid-Osteoma.—Hamilton [1] reviews the literature and the clinical picture and points out that sclerosis may obscure the nidus on roentgenologic examination unless overexposure and several views are employed. He further brings out that more sclerosis occurs when the lesion is in the cortex than when it is in the medulla. In differential diagnosis, osteoid-osteoma may be distinguished from Garré's osteomyelitis, Brodie's abscess, osteogenic sarcoma or Ewing's tumor. Hamilton reports 5 cases; in 2 the lesion occurred in the tibia, and in 1 each it occurred in the humerus, the talus and the second cervical vertebra.

[ED. NOTE.—We agree that roentgenograms made at several different angles will often bring out the nidus, which otherwise might be overlooked.]

Jaffe [2] reports that an osteoid-osteoma is a small, oval or round, nidus-like benign neoplasm of bone, usually not more than 1 cm. in diameter. Men are affected twice as often as women. A majority of patients in the author's series were between the ages of 11 and 24 years; extremes were 1½ and 49 years. The symptoms, usually of six to twenty-four months' duration, are predominantly pain (often worse at

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From the Section on Orthopedic Surgery, Mayo Clinic.

1. Hamilton, J. F.: Osteoid Osteoma, with Case Reports, Surg., Gynec. & Obst. **81**:465-474 (Nov.) 1945.

2. Jaffe, H. L.: Osteoid-Osteoma of Bone, Radiology **45**:319-334 (Oct.) 1945.

night) and, less often, limping and mild local swelling. Examination may reveal slight tenderness, swelling and muscular atrophy. The lesion generally occurs in the femur or tibia, although any bone may be affected. On roentgenologic examination, the nidus appears as a radiolucent (occasionally radiopaque) area in the cortex or medulla, with more or less sclerosis surrounding it, although sclerosis may be absent early in the disease. The microscopic picture of a well advanced lesion is that of osteoid, trabeculae of new osseous tissue and a substratum of highly vascular connective tissue. Treatment is complete excision or curettage; the lesion recurs only if any part of the nidus is left. Irradiation has not been tried. Data in 62 proved cases, as well as case reports in 5 of these, are presented.

[ED. NOTE.—This is an important series of cases reported by Jaffe, the discoverer of the lesion. Formerly osteoid-osteoma was frequently diagnosed as sclerosing osteitis of Garré, and some persons still prefer that classification. However, there are enough cases now recorded to show that the lesion is a distinct clinical entity, which is amenable to surgical treatment. In 1944, in a report of 80 cases of chronic sclerosing osteitis, one of us (H. W. M.) included a number of cases in which the condition would now be classified as osteoid-osteoma. It is always advisable to examine microscopically for signs of osteoid-osteoma all material removed at operation in cases of sclerosing lesions of bone. Whenever possible, the entire lesion should be excised and sections so cut that they include tissue from the nidus. Fortunately, the lesion is benign, the treatment is surgical excision and the results remain good, irrespective of terminology employed. Two reports on chronic sclerosing osteitis are recommended (Meyerding, H. W.: *Tr. West. S. A.* **52:** 545-564, 1944; *S. Clin. North America* **40:***762-779* [Aug.] 1944)].

Osteoma.—Kautz [3] presents a classification of primary tumors of the knee joint and a historical review of osteoma of the knee joint. Kienbock, in 1934, concluded that osteoma occurs rarely in other joints, that there is only slight functional impairment, that incarceration does not occur and that blood vessels and surrounding skeletal parts are never invaded. The lesion is a new growth of synovial origin. Kautz adds 4 cases to the 2 previously reported in American literature; Kautz's cases are almost identical with the others in respect to history, clinical course and roentgenologic findings. In each instance, the tumor was located just beneath the patella and had no osseous connection with neighboring bones. Three patients admitted repeated traumatism. The microscopic appearance was that of a true bony tumor; the tumor in each case was made up of highly organized osseous tissue and evi-

3. Kautz, F. G.: Capsular Osteoma of Knee Joint: Report of Four Cases, Radiology **45:**162-167 (Aug.) 1945.

dently had been a living body in which active proliferation, but no malignant change, had occurred. A well delineated shadow of bony density, with a cancellous pattern and a dense outer shell, was seen on the roentgenograms. Differential diagnosis is discussed.

METABOLIC LESIONS

Eosinophilic Granuloma.—Solomon and Schwartz [4] state that eosinophilic granuloma is a benign, destructive bone lesion, which may be single or multiple. Large mononuclear histiocytes and usually eosinophils are seen microscopically, the presence of the eosinophils usually indicating an early stage of the process. Flat bones are involved more often than the other types. Complaints are mainly of pain, swelling and local tenderness; the duration may be from a few days to several months. Slight fever and leukocytosis may be present. The roentgenograms reveal a destructive, well localized lesion, which may erode the cortex. Untreated, it resolves within a year. The duration is the same whether the lesion is treated by irradiation or by curettage. Many pathologists believe that the condition is related histologically to Letterer-Siwe disease and to Christian-Schüller disease. In differential diagnosis the possibility of benign giant cell tumor, solitary bone cyst and Ewing's tumor, among others, must be considered. A case is reported in which the disease occurred in the femur of a white patient of 17.

Michael and Norcross [5] report 2 cases of eosinophilic granuloma; in one the lesion involved the skull, and in the other it affected the ninth thoracic vertebra, adjacent tissues and the thoracic part of the cord. The lesions were unrelated to trauma; some infectious agent may have been causative. The findings did not relate the lesions to Letterer-Siwe disease or to Christian-Schüller disease. Operation is advisable for diagnosis and treatment. Irradiation is a valuable adjunct. However, spontaneous healing has been known to occur.

[ED. NOTE.—We believe that these reports on eosinophilic granuloma are of great interest, though the series is small. We think that Letterer-Siwe disease and Christian-Schüller disease are probably different stages of development of the same condition.]

VASCULAR TUMORS

Hemangioma.—Zadek [6] reports a case of hemangioma in a woman of 23, who had undergone an exploration of the knee ten years pre-

4. Solomon, H. A., and Schwartz, S.: Eosinophilic Granuloma of Bone, J. A. M. A. **128**:729-731 (July 7) 1945.

5. Michael, P., and Norcross, N. C.: Eosinophilic Granuloma of Bone, U. S. Nav. M. Bull. **45**:661-668 (Oct.) 1945.

6. Zadek, I.: Painful Knee Due to Hemangioma (Cured by Operation), Bull. Hosp. Joint Dis. **6**:29-32 (April) 1945.

viously because of pain (diagnosis was uncertain). Zadek reexplored the knee and removed a hemangioma from the musculotendinous junction of the vastus medialis muscle; he reports the patient cured.

Webster and Geschickter [7] state that hemangioma of the tendon sheaths is rare. In 1937, Harkins reviewed the reports of 25 cases in the literature; in only 4 cases was the lesion in the fingers. In the case reported by the authors, the lesion appeared as a painful swelling at the base of the left index finger. At operation, a small, lobulated tumor mass, which had apparently originated in the sheath of the flexor tendon, was removed. The result was good.

Arkin [8] refers to Harkins' report of 1937 and reports a case in which a hemangioma was completely enclosed in the sheath of the interior tendon of the left tibia. The lesion had been present for twenty years. It was a painless, slowly growing lump; at first it had been the size of a pea, but at the time Harkins saw the patient it was 10 by 5 cm. The entire lesion was successfully removed, and six months after operation the result was excellent.

[ED. NOTE.—The complete excision of benign vascular tumors should result in cure. When surgical removal is incomplete or inadvisable, roentgen therapy may be employed.]

Williams [9] briefly reports a case of Ewing's tumor of the shaft of the femur in an adolescent boy. An illustration shows diffuse involvement of the whole right innominate bone. The author points out that Ewing's tumor is most frequently seen in the shaft of the femur, tibia or humerus but may occur in the jaw, the scapula and/or in the pelvic bones.

TUMORS OF SYNOVIAL MEMBRANE

Tumors of synovial membrane are extremely rare. To the total number previously reported in the literature (about 62 cases) Hartz [10] adds 3 cases in which the lesion was of a malignant type. In 2 cases, the tumor originated in the knee joint and in 1, in the foot, probably in a tendon sheath. In 2 cases, the tumor cells were partially differentiated into elements resembling epithelium, whereas in 1 case, the tumor had to be considered as predominantly histiocytic. As in many mesenchymal tumors, spindle cells may be present. Thus, the characteristics of

7. Webster, G. V., and Geschickter, C. F.: Benign Capillary Hemangioma of Digital Flexor Tendon Sheath: Case Report, Ann. Surg. **122**:444-448 (Sept.) 1945.

8. Arkin, A. M.: Hemangioma of Tendon, Am. J. Surg. **69**:133-134 (July) 1945.

9. Williams, E. R.: Ewing's Tumors (Diffuse Endothelioma of Bone), Brit. J. Radiol. **18**:198 (June) 1945.

10. Hartz, P. H.: Cancerous Synovial Tumors, Arch. Path. **40**:88-93 (Aug.) 1945.

fibrosarcoma or of spindle cell sarcoma may mask true sarcoma of the synovial membrane. All 3 patients were treated by high amputation. In 2 of the 3 cases, the malignant nature of the disease was recognized only on microscopic examination.

FIBROBLASTIC TUMORS

Winderman [11] reports a case of expanding trabeculated tumor which involved almost the entire first metatarsal bone of the right foot of a white man of 56. The tumor, on gross examination after excision, was found to consist of grayish, fatty material, arranged in lobules of various sizes inside the bone. The pathologic examination revealed a fibromyxoma. A bone graft successfully filled the defect, and Dr. Jaffe was of the opinion that the tumor would not recur. Winderman mentions that the same type of tumor was seen at a New York hospital in 5 other cases; the tumor was located in the femur in 3 of the 5 cases and in the tibia and in a metatarsal bone of the foot in 1 case each.

GIANT CELL TUMOR

Foote and Fett [12] review the literature on benign giant cell xanthoma of the knee joint, and also describe the clinical and anatomic appearance of the lesion. The treatment is wide surgical extirpation. Recurrence of the tumor has been described, but in no instance has malignant transformation been reported. A case is reported in which the lesion occurred in a man of 22; he gave a history of pain and "locking" of three weeks' duration. A palpable mass, about 1 cm. in diameter, was located at the anteromedial aspect of the knee joint. Roentgenographic studies of the knee in this case were of little value. The gross and microscopic features of the tumor are presented.

Jaffe [13] reports a study of pertinent anatomic material, which was made to decide the exact basis on which the diagnosis of giant cell tumor should be made. A tendency was observed to class with giant cell tumors various lesions which contain giant cells, without consideration of the quantity and grouping of these cells or the anatomic character of the lesion. The author emphasizes that this type of tumor should be considered a true neoplasm and a serious one. He also presents a discussion of histologic and gross appearance, clinical and roentgenographic peculiarities and treatment. As problems of differential diagnosis he discusses, first, solitary bone cyst, which differs from giant cell tumor

11. Winderman, A. I.: Fibromyxoma of the Metatarsal Bone, Bull. Hosp. Joint Dis. **6**:70-74 (April) 1945.

12. Foote, R. F., and Fett, H. C.: Benign Giant Cell Xanthoma of the Knee Joint, Am. J. Surg. **70**:234-236 (Nov.) 1945.

13. Jaffe, H. L.: Giant Cell Tumor of Bone: Problems of Differential Diagnosis, Bull. Hosp. Joint. Dis. **5**:84-91 (Oct.) 1944.

chiefly in that it occurs in children and adolescent persons and secondarily in that it occurs in a different location and has a different anatomic appearance; second, nonosteogenic fibroma of bone, which, like solitary bone cyst, occurs mostly in older children, is located usually in the shaft and presents a different microscopic picture; third, benign chondroblastoma of bone, which differs mainly in its fuzzy and mottled appearance in the roentgenogram, indicating that calcification is going on within the lesion, and, fourth, a solitary focus of fibrous dysplasia, which constitutes a real problem in differential diagnosis.

Andersen [14] discusses theories of the pathogenesis, as well as the possibility of malignant transformation, of giant cell tumor and osteitis fibrosa. He reports 16 cases of giant cell tumor in various locations; in only 1 did the lesion undergo malignant transformation to osteogenic sarcoma. The case was that of a man of 20, who had a clinically and roentgenologically benign-appearing giant cell tumor in the head of the right humerus. Tissue for biopsy, obtained by trephining, gave no sign of malignancy, but three years after irradiation the lesion had become an osteogenic sarcoma, which proved fatal. The author also mentions another case, that of a man of 51, in which a lesion in the right lateral condyle of the femur masked itself as a benign giant cell tumor for seven years but probably was primarily malignant; death occurred from osteogenic sarcoma. Roentgen therapy was of little effect in this series of epiphysial giant cell tumors. The author further reports a series of 13 cases of osteitis fibrosa and a series of 19 cases of epulis. Histologic examination did not enable the author to group the giant cell tumors, but there appeared to be a gradual transition to osteitis fibrosa. He expresses the belief that biopsy should always be performed before treatment is instituted.

Johnson and Lyford [15] describe a rather conservative operation for benign giant cell tumor in the distal end of the femur in persons in which the articular cartilages of the knee joint are intact; the operation is a compromise between simple grafting and radical amputation. The tumor is removed by curettage; the cavity is then cauterized with phenol U.S.P., the fragments are telescoped and the wound is closed tightly, without drains. Function of the knee after healing is good, and patients are able to bear full weight on the leg. There is, however, a shortening of the leg of 1 to 3 inches (2.5 to 7.5 cm.), which is corrected by a lift on the shoe. The healing time is somewhat longer than

14. Andersen, S. R.: The Malignancy of Giant Cell Tumors: A Study on Giant Cell Tumors and Allied Affections in Bone with Reference Specially to Their Malignancy, Acta radiol. **26**:11-35, 1945.

15. Johnson, R. W., Jr., and Lyford, J., III: Treatment of Benign Giant-Cell Tumor in the Lower Third of the Femur by Curettage and "Telescoping" the Fragments of Bone, J. Bone & Joint Surg. **27**:557-561 (Oct.) 1945.

that for a comminuted supracondylar fracture of the femur. Six similar cases, all in women, are reported; successful results were obtained in all.

[Ed. Note (H. W. M.).—The number of articles appearing in the literature demonstrates the great interest of the medical profession in the subject of giant cell tumor of the bone. It must be remembered that giant cell tumor may be benign or malignant. Occasionally one encounters a case in which the diagnosis is benign giant cell tumor and in which malignancy develops later; I classify this type of lesion as secondary giant cell sarcoma. However, I designate the type which is proved by microscopic examination to be malignant at surgical exploration, before any type of treatment has been instituted, as primary malignant giant cell sarcoma. When one keeps in mind the terms, "benign giant cell tumor" for the benign group and "malignant giant cell sarcoma" for the malignant group, there is less confusion. I believe that roentgen therapy of benign giant cell tumor may prove of increasing value; however, whenever it is possible, and when carried out in the proper surgical environment, complete excision, followed with chemical cauterization and packing of the cavity with autogenous bone grafts, gives the best result. Certainly such operations merit a most exact aseptic technic and should be performed by an experienced orthopedic surgeon. It is unfortunate that some lesions occur in such locations that surgical treatment is precluded; in such instances roentgen therapy is indicated. My associates and I believe that microscopic examination by an expert pathologist is advisable in all cases after operation.]

SARCOMA SECONDARY TO ROENTGEN THERAPY

Hatcher[16] reviews the literature on cases of development of sarcoma of the bone after irradiation of overlying soft tissue lesions (for example, abscesses) and lists reports of cases in animals, in which osteogenic sarcoma was induced by local implantation of radium and mesothorium, or by ingestion of radium. In the literature there were reports of 24 cases in which sarcoma of bone occurred after irradiation; in 17 the lesions resulted from treatment of tuberculous arthritis. Hatcher presents 3 cases in which sarcoma of bone resulted from irradiation of bone in the treatment of earlier independent tumors. Two lesions developed in bones adjacent to separate bones which had been irradiated for giant cell tumor, that is, in the ulna and in the fibula, respectively, after treatment of radial and tibial lesions. In the third case, the lesion was located in a rib and had occurred after radical mastectomy and irradiation for carcinoma. The sarcoma in each case was of cartilaginous origin, and the time of appearance was seven years after irradiation in 1 case and eleven years after, in the other 2.

16. Hatcher, C. H.: The Development of Sarcoma in Bone Subjected to Roentgen or Radium Irradiation, J. Bone & Joint Surg. **27**:179-195 (April) 1945.

Kenney [17] reports the second case in the literature of a pathologic fracture which occurred in a patient with polymorphous cell sarcoma (the malignant phase of giant and follicular cell lymphoma). The patient was seen because of a pathologic fracture, which had healed; subsequently three more fractures in the same femur healed, but the patient died of generalized skeletal metastases before a last fracture of the same bone had the opportunity of healing. The findings at biopsy and necropsy confirmed the diagnosis of giant and follicular cell lymphoma. Most of the lymphoid tissue in the body and most of the bones were involved; the liver and spleen were spared.

OSTEOGENIC SARCOMA SECONDARY TO PAGET'S DISEASE

Burr [18] reports a case of osteogenic sarcoma of the scapula, secondary to Paget's disease. The patient was a man of 59. Death occurred about seven months after the onset of symptoms. Tissue removed from the mass in the axilla was examined by a pathologist, who confirmed the diagnosis of osteogenic sarcoma. Burr also discusses blood chemistry in Paget's disease, osteogenic sarcoma, metastatic carcinoma and hyperparathyroidism. He reviews the literature on Paget's disease and the findings with respect to malignant transformation, citing Gutman and others, Coley and Sharp, Codman, Kay, Paget, von Albertini, Nichols, King and Armstrong, Robinson, and Albright, Aub and Bauer.

Burr discusses the close association between Paget's disease and sarcoma and concludes that Paget's disease apparently predisposes to sarcoma. He discusses the role that blood chemistry plays in the differential diagnosis of hyperparathyroidism, Paget's disease and secondary malignant disease, and states the belief that treatment of osteogenic sarcoma by irradiation, operation or both is ineffective.

FIBROSARCOMA

Milch [19] reports a case of fibrosarcoma (ungraded), in which the lesion was developing primarily in the left sternocleidomastoid muscle of a girl, 21 months of age. A breech delivery had occurred at full term, after a difficult labor; the baby lost the use of the left arm for one month after birth and had a persistent tilt of the head to the left. Surgical excision of the tumor was followed by roentgen therapy, with no

17. Kenney, W. E.: Polymorphous-Cell Sarcoma, the Malignant Phase of Giant-Follicle Lymphoma, with Generalized Skeletal Involvement and Multiple Pathological Fractures: Report of a Case, J. Bone & Joint Surg. **27**:668-673 (Oct.) 1945.

18. Burr, R. C.: Osteogenic Sarcoma Developing on Paget's Disease, Canad. M. A. J. **53**:262-265 (Sept.) 1945.

19. Milch, H.: Torticollis Due to Sarcoma of Sterno-Mastoid Muscle, Bull. Hosp. Joint Dis. **6**:61-63 (April) 1945.

evidence of recurrence or metastasis six months after operation; good motion of the head was obtained.

[ED. NOTE.—This is the first case of fibrosarcoma that I have heard of in which the lesion occurred in the sternocleidomastoid muscle of a baby who had torticollis after a difficult labor. Usually the swelling results from hematoma and degenerated muscle, with fibrosis and shortening which produce contracture that maintains the tilted position of the head.]

METASTATIC TUMORS

Carcinoma.—Singer [20] reports a case of large, ulcerating basal cell carcinoma on the right side of the face, with a secondary ulcerative lesion in the right submaxillary region. The patient was a woman of 72. She fell and sustained a fracture of the upper third of both femurs. At necropsy, the histologic examination of portions of the femur and ilium indicated much tissue similar to that of secondary basal cell carcinoma in the substantia spongiosa, cortex and periosteum. In a search of the literature Singer found only 1 other case, reported by Willis, in which metastasis of basal cell carcinoma resulted in pathologic fracture.

Brooke and Thomason [21] review the literature and point out that sarcoma of the uterus is a rare neoplasm, occurring in probably not more than 1 per cent of patients who are operated on for uterine fibromyoma. Metastatic lesions from sarcoma of the uterus occur most commonly in the lungs, peritoneum, lymph nodes, liver and kidneys. Little has been written concerning metastasis of uterine sarcomas to bone. The authors found reports of only 3 cases in the literature; they report the fourth proved case in which metastatic lesions occurred in the femur.

Smithers and Rhys-Lewis [22] discuss three groups of cases of carcinoma of the uterus in which destruction of bone occurred. They also discuss blood-borne metastatic lesions, the relatively frequent direct invasion of bone from a primary lesion or from the lymph nodes and the necrosis of bone which sometimes follows irradiation. The importance of limiting the radiation for treatment of carcinoma of the cervix to the tissue involved, in order to obviate the risk of damage to bone, is emphasized. The authors report a case in which roentgen therapy applied to large fields resulted in necrosis of bone and skin, and eventually in death.

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20. Singer, A.: Basal-Cell Carcinoma of Face with Remote Metastases and Pathological Fractures, Brit. J. Surg. **32**:537-538 (April) 1945.

21. Brooke, W. S., and Thomason, J. R.: Leiomyosarcoma of the Uterus with Metastasis to the Femur: Report of a Case and Review of the Literature, Arch. Surg. **51**:120-124 (Sept.) 1945.

22. Smithers, D. W., and Rhys-Lewis, R. D. S.: Bone Destruction in Cases of Carcinoma of the Uterus, Brit. J. Radiol. **18**:359-362 (Nov.) 1945.

Bancroft and Beal [23] report a case of eight pathologic fractures, five of which definitely healed. Only one of the fractures was subjected to roentgen therapy. The fractures occurred during a five year period; the patient had had radical amputation of the breast for medullary and scirrhous carcinoma, with axillary metastasis. The union of the first pathologic fracture of the femur was strong enough to permit walking without difficulty. Later the patient had a fracture of the same bone, but at a different location.

[ED. NOTE.—Roentgen therapy should always be given at the hands of a well trained roentgenologist. All experienced surgeons have seen patients with ulcerative actinodermatitis following roentgen therapy. Hatcher reports the occurrence of sarcoma after irradiation; this further illustrates the fact that one cannot always judge the end results of such treatment.]

Rhabdomyosarcoma.—Viets and Wittenborg [24] report a case of rhabdomyosarcoma in a man of 49; diagnosis of spindle cell sarcoma was made at biopsy. The lesion occurred beneath the right shoulder blade. The patient had complete dysfunction of the spinal cord (retention of urine, paralysis, and loss of sensation up to the level of the tenth thoracic vertebra). Death occurred fourteen months after discovery of the tumor. Metastatic lesions were present in the lungs and the right kidney; erosion of the spinal column and compression of the cord at the tenth thoracic vertebra were observed.

CHORDOMA

Brindley [25] reviews literature and reports 3 cases of sacral and presacral tumors: a chordoma, an ependymoma and a dermoid cyst. Tumors in this location are rare and are of many pathologic types, since they usually arise from vestigial embryonal tissue and generally are either of low grade malignancy or benign; they usually are chordomas, dermoids, ependymomas, teratomas, Ewing's tumors, giant cell tumors, neurofibromas or fibrosarcomas. Early diagnosis is difficult; the value of digital rectal examination is stressed. Symptoms are usually those of pressure on neighboring structures, including the rectum and bladder. Roentgenograms may or may not be helpful. Chordomas occur twice as often in men as they do in women, while dermoids have never been reported in men. Location, size, duration, pathologic characteristics

23. Bancroft, F. W., and Beal, J. M.: Healing of Pathological Fractures Through Metastases from Carcinoma of the Breast, Am. J. Surg. **69**:236-237 (Aug.) 1945.

24. Viets, H. R., and Wittenborg, M. H.: Rhabdomyosarcoma, Arch. Path. **40**:179-181 (Sept.) 1945.

25. Brindley, G. V.: Sacral and Presacral Tumors, Tr. South. S. A. **56**:337-352, 1944.

and extent of spread of the tumor into the surrounding tissues are factors which affect treatment and prognosis. Treatment of chordomas has given almost routinely poor results, since the lesions tend to recur locally. Treatment of presacral and sacral tumors consists of: (1) wide excision through a posterior approach (Kraske's position); (2) immediate examination of frozen sections of tissue taken from the line of incision; (3) use of the cautery knife to burn the edges of the wound in cases of malignancy (this procedure is stressed) and (4) roentgen therapy in cases of malignant tumor. More radical primary excision of these tumors is advocated; it is brought out that much of the lower portions of the sacrum, the coccyx, the lower three sacral nerves and the neighboring muscles and viscera can be removed without causing severe disability.

Robbins [26] reports a case of chordoma in which the lesion occurred in the lumbar vertebrae of a white man of 41. The author states that only 13 cases of chordoma of the lumbar region have been previously reported. The patient in the case died nine days after exploratory laparotomy, which revealed a large mass adherent to many abdominal organs. Microscopically, the mass exhibited the two constant features of chordoma, abundant mucous matrix and large physaliferous cells. Despite evidence of cellular anaplasia and mitotic activity, the tumor characteristically was carcinomatous only locally, with no signs of metastasis. For this reason, recognition of such tumors from a pathologic standpoint is important, as radiation can be used effectively to control the growth at the primary site, with reasonable assurance that metastasis will not occur.

MYOBLASTOMA

Orr [27] reports a case in which the clinical diagnosis was lipoma but in which, on microscopic examination of tissue at operation, the lesion proved to be a myoblastoma. Myoblastoma was associated with frank carcinoma in 28 per cent of cases and with epithelial hyperplasia in 45 per cent.

GLOMUS TUMORS

German [28] reports a case of glomus tumor in an unusual location in the deeper tissues. The case was that of a man of 39, who had a slowly growing, painful, tender mass in the posterior portion of the upper part of the right arm. At operation, a sharply demarcated, encapsulated mass, located in the triceps muscle, was removed. Histologically, the lesion

26. Robbins, S. L.: Lumbar Vertebral Chordoma, Arch. Path. **40**:128-132 (Aug.) 1945.

27. Orr, T. G., Jr.: Myoblastoma: Case Report, Ann. Surg. **122**:122-125 (July) 1945.

28. German, W. M.: Glomus Tumor of Triceps Muscle, Am. J. Clin. Path. **15**:199-201 (May) 1945.

fulfilled the criteria of an organoid structure in regard to the central blood supply, the relation of the epithelioid tumor cells to the blood supply and the presence of a rich reticulum and an occasional neurofibril.

[ED. NOTE.—We have recently removed 3 glomus tumors; 1 was located beneath a finger nail and was of eleven years' duration, another occurred in the side of a finger, and the third was situated distal and mesial to the left olecranon process. All tumors had caused severe pain over a period of years, and all patients obtained a cure after surgical excision.]

MISCELLANEOUS

Grout,[29] in October 1944, stressed the difficulty in roentgenologic interpretation of lesions of bone and remarked on the difficulties and misunderstandings that occur unless the roentgenograms are interpreted in conjunction with the clinical findings. He pointed out the need for better follow-up data and for closer cooperation between the roentgenologist and the clinician. Some most interesting roentgenograms are shown with this brief abstract.

[ED. NOTE.—We are in accord with the author. Whereas the roentgenologic interpretation of bone lesions permits a high percentage of correct diagnoses, there yet remain inoperative cases in which the true nature of the lesion is not determined until death, when necropsy reveals the findings. This may be true also, to a lesser extent, in cases in which operation and microscopic examination have been performed.]

29. Grout, J. L. A.: Bone Tumours and Their Radiological Implications: President's Address, Proc. Roy. Soc. Med. **38**:345-347 (May) 1945.

REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomaly.—Herbst [1] states that observations for a period of six years have resulted in an experience which indicates that the posterior location of the renal pelvis is important in the case of patients who have ptotic kidneys. Every patient operated on during the six year period had this condition.

In 13 cases nephrectomy was performed, and in 2 cases resection of the lower pole of the kidney was done. Diagnostic features, from a roentgenologic standpoint, were the lateral location of the course of the ureter as compared with the medial border of the renal pelvis and the gun barrel effect of the ureter branching off posteriorly. Posterior location of the renal pelvis is, in the opinion of Herbst, the result of a congenital malformation. The ureteral bud fuses in such a way that even though the kidney itself may rotate normally the renal pelvis and ureter come out of the posterior surface instead of the medial border.

Neoplasm.—Dark cell adenocarcinomas of the renal cortex are rarely seen, and the literature on their origin, growth and prognosis is scant.

1. Herbst, W. P.: The Posteriorly Located Renal Pelvis Associated with Ptosis, J. A. M. A. **137**:775 (June 26) 1948.

Fryfogle, Dockerty, Clagett and Emmett [2] present a specific group of tumors that shows a constant microscopic cellular differentiation, the dark cell adenocarcinomas, and correlate the clinical, surgical and post-operative records with their pathologic study. They examined 768 malignant neoplasms of the renal cortex grossly and microscopically. After the microscopic uniformity of these lesions was established, the tumors were graded, classified by their predominant pattern and stained for fat and reticulum. Stains for glycogen were obtained on the last specimen before fixation with formaldehyde. Clinic records of acceptable cases were reviewed, and a comparison was made between tumors and a similar series of the clear cell type of tumor.

Of 29 tumors, which were finally selected as dark cell adenocarcinomas of the kidney, only 3 presented the opaque yellow luster of the typical hypernephroma. The tumor capsule was grossly evident in 13 and ill defined in 11 cases. In 5 cases spread of the lesion to involve the pelvis, the entire cortex and the proximal structures made the gross study of a limiting capsule impracticable. Encapsulation of the 13 previously mentioned tumors was marked, and all were undergoing necrosis to the extent of 40 to 70 per cent of the bulk of the tumor. Of the 29 tumors, 7, or 24.1 per cent, invaded the pelvis; 5, or 17.1 per cent, had broken through the true renal capsule to involve adjacent structures, and in 11, or 37.9 per cent, tumor thrombi were found in the renal vein. Seven tumors (24.1 per cent) were found in the upper pole, and 7 were found in the lower pole. Thirteen tumors (45.0 per cent) originated in the middle portion of the kidney. Two tumors (6.8 per cent) involved the entire kidney.

The tumors were chosen because they represented neoplasms composed entirely of one type of cell. They occurred in four different patterns. Six tumors had a tubular arrangement in which all the cells were of fairly adult type. These represent an apparent hyperplasia of the parent structure. The tubules were of uniform size and shape. Little microscopic evidence of necrosis was present. Papillary formation was present in 16 tumors. In 4 cases of dark cell cortical carcinomas the pattern was so multivariant that they were placed in a miscellaneous group and no attempt was made to classify them.

The tumors were graded after the method of Broders. Eight were graded 1; 14 were graded 2; 6 were graded 3, and 1 was graded 4. The average age, 49.8 years, is slightly less than the age reported for the series of patients with hypernephromas. The greatest number of patients (41.5 per cent) were 40 to 49 years of age. In contrast, the greatest number of patients having hypernephromas (43.5 per cent) were 50 to

2. Fryfogle, J. D.; Dockerty, M. B.; Clagett, O. T., and Emmett, J. L.: Dark-Cell Adenocarcinomas of the Kidney, J. Urol. **60**:221 (Aug.) 1948.

59 years of age. Sixteen (55.2 per cent) of the patients were men, and 13 (44.8 per cent) were women, which is a marked difference from the ratios of 2:1 or 3:1 in the series of hypernephromas. Among the 10 patients whose chief complaint was of a mass the duration of the symptom varied from five years to six weeks. The average duration was 18.7 months. Four of the 10 patients did not have symptoms related to the genitourinary tract. Among the 8 patients who complained of hematuria the duration of the symptom was from nine years to three weeks; the average duration was 18.3 months. Among the 3 patients who complained chiefly of pain the duration of the symptom was from three years to six weeks; the average duration was 15.2 months. The diagnosis of dark cell adenocarcinomas cannot be made, as such, preoperatively, but it should be suspected on alteration of gross color and ill defined encapsulation and can be proved by the presence of only dark granular cells on multiple microscopic sections.

The tumors differ from mixed cell and clear cell adenocarcinomas in that they contain little or no intracellular fat, they appear to occur more frequently in women than in men and a mass is the symptom of which most frequent complaint is made. They frequently calcify, and, regardless of size, if the tumor is removed before extrarenal extension occurs, the patients, especially the women, survive long terms. Prognosis in this small series was somewhat better than for hypernephromas. Of 29 patients, 8 underwent operation within the last five years; the condition of 1 patient was followed for only three years, which left 20 patients to be considered for calculation of a five year survival rate. Ten patients (50 per cent) lived five or more years after operation.

Heckel and Penick [3] report the case of a woman 47 years of age having a mixed tumor of the kidney. The term "mixed tumor" includes many tumors of varying types of tissue, but the histogenesis probably is similar. The tumors are slow growing and make their appearance later than the allied but undifferentiated Wilms's tumors.

Campbell [4] presents 2 cases of true primary bilateral Wilms's tumor of the kidney. Occurrence of the tumor appears confirmatory of the congenital nature of the lesion. In the first instance the preoperative diagnosis had been bilateral renal cystic disease but the diagnosis of tumor was confirmed by operation and by histologic examination. In the second case these conditions coexisted with other grave anomalies and were unexpected postmortem findings.

3. Heckel, N. J., and Penick, G. D.: A Mixed Tumor of the Kidney: Lipo-Myo-Hemangioma, J. Urol. **59**:572 (April) 1948.

4. Campbell, M. F.: Bilateral Embryonal Adenomyosarcoma of the Kidney (Wilms Tumor), J. Urol. **59**:567 (April) 1948.

Lymphosarcoma.—Gibson [5] reports 3 cases of renal involvement by lymphosarcoma. Lymphosarcoma of the kidney is a misnomer, since primary involvement of this organ probably never occurs. Involvement of the kidneys may occur either by metastasis or by direct invasion from neighboring foci of the disease. The clinical manifestations fall into three groups: (1) those in which there may be initial or incidental symptoms of renal colic as a result of constriction or strangulation of the ureter by retroperitoneal lymphoma, (2) those in which the kidney is involved to such a degree that they are mistaken for primary renal neoplasms and (3) those in which the clinical findings point to a primary retroperitoneal lymphosarcoma with secondary involvement of the kidneys.

Renal involvement by lymphoma may be unilateral or bilateral. It may occur as a diffuse interstitial infiltration of lymphoid cells; there may be multiple nodular involvement, or a single large metastatic nodule and lastly the kidney may be engulfed by lava-like flow of lymphomatous tissue more or less completely surrounding it with or without direct invasion of the parenchyma.

Diagnosis offers difficulties because of the great variety of pathologic manifestations of lymphomas and their origin in deeply placed mediastinal mesenteric or retroperitoneal glands. Superficial adenopathy when detected usually implies a late stage of the disease.

Although cure of lymphomatous involvement of the kidney has not been reported, in general the outlook for patients having lymphomas is not entirely hopeless. If the lymphoma is confined to an accessible single mass, a condition dependent on early diagnosis, complete surgical extirpation of the primary focus offers an excellent chance for obtaining a cure. Irradiation and treatment with nitrogen mustards are considered valuable adjuvants to surgical treatment, in addition to their value in palliation.

The term "lymphosarcoma of the kidney" should be replaced by the more correct designation of "renal lymphomatosis."

Taylor [6] reports a case of hypernephroma associated with massive bilateral adenoma of the adrenal glands. The patient, a man 54 years of age, had been treated for sciatica. Roentgenograms showed evidence of extensive destructive changes in the left ilium and in the right sacral wings; destructive changes probably had occurred in several of the vertebral bodies, notably the seventh and twelfth thoracic and second lumbar vertebrae. A considerable portion of the seventh dorsal body had col-

5. Gibson, T. E.: Lymphosarcoma of the Kidney, J. Urol. **60**:838 (Dec.) 1948.

6. Taylor, J. A.: Extensive Metastasizing Hypernephroma Associated with Massive Bilateral Adenoma of the Adrenal, J. Urol. **59**:557 (April) 1948.

lapsed. Destructive and productive changes were seen in the posterior portion of the sixth rib on the left side. The changes were characteristic of extensive metastasis of carcinoma. The prostate did not show evidence of malignant disease, and hypernephroma was considered, although on palpation the kidneys did not seem to be enlarged. Cystoscopic studies were precluded because of the extensive vertebral involvement and the paraplegia which had developed. Removal of the lump on the chest over the sixth rib and the pathologic study of it showed a compact overgrowth of cellular tissue interspersed with a few bony trabeculae. The tumor was composed of glandular epithelial cells forming complex, but distinctly papillary, structures. A diagnosis of metastatic papillary carcinoma was made. The probable primary site of the tumor is a hypernephroma or a clear-celled carcinoma of the kidney. The patient died shortly after examination.

Necropsy revealed that both adrenals were considerably enlarged and replaced by golden yellow cortical tumor tissue. On each side of the adrenals, firm, nodulated, broad, thick masses of tumor had formed, surrounded by a considerable amount of fat. On the left side the tumor which replaced the adrenal gland measured 11 by 4 by 2.5 cm.; on the right side the solid nodular tumor replacing the adrenal was 10 by 3 cm. Both adrenal tumors were entirely discrete and separate from the kidneys. The kidneys were embdded in large fatty capsules. They were normal in size; the left measured 13 by 6 by 4 cm., and the right measured 12 by 5 by 4 cm. A circumscribed tumor projected from the hilus of the right kidney and was situated more in the lower than in the upper half. This projecting tumor appeared to be encapsulated and measured 4.5 by 2.5 cm.; it was a hypernephroma.

Mann [7] reports a case of spontaneous disappearance of pulmonary metastatic lesions after nephrectomy for hypernephroma. The patient, a man aged 62 years, with a history of eight months of progressive weakness, productive cough with dark sputum and loss of weight, was pale and thin and had marked secondary anemia. Results of urinalysis, a chemical examination of the blood and a Wassermann test were normal. A roentgenogram of the thorax showed multiple metastatic nodules, 1 to 4 cm. in diameter, scattered throughout both lungs. An intravenous pyelogram, taken in searching for a primary focus, showed evidence of a mass compressing the calices of the lower pole of the left kidney, typical of tumor. The presence of the mass was confirmed by a retrograde pyelogram. Nephrectomy was performed, and a tumor the size of an orange was found which occupied the midportion of the kidney. The

7. Mann, L. T.: Spontaneous Disappearance of Pulmonary Metastases After Nephrectomy for Hypernephroma: Four Year Follow-Up, J. Urol. **59**:564 (April) 1948.

pathologic report was that the specimen was a malignant Grawitz tumor (hypernephroma), with invasion of the small veins and lymphatic vessels. The postoperative course was uneventful. Seven weeks after operation a roentgenogram of the thorax showed increased and extensive areas of pulmonary metastasis. A roentgenogram of the thorax six months later showed complete disappearance of the nodules. One year later a roentgenogram showed that the lungs were still free of metastatic processes. Roentgenograms of the bony pelvis and long bones taken on Dec. 7, 1946, did not show evidence of metastasis.

Ferris and Daut [8] report a case of epithelioma of the pelvis of a solitary kidney treated by electrocoagulation. The patient, a man 61 years of age, entered the Mayo Clinic on June 6, 1946, complaining of continuous gross hematuria of six months' duration. The history was noncontributory. One and a half years previous to his coming to the clinic he had noted bloody urine, but this condition had subsided spontaneously after four days. The second episode of bleeding had begun six months before his admission to the clinic and had continued unabated. Clots had not been noted in the urine, and a history of renal colic could not be elicited. Physical examination revealed a pale, edentulous white man. No masses were palpated in the abdomen; the heart and lungs were normal, and the prostate was normal to palpation by rectum. A simple roentgenogram of the abdomen showed evidence of a large renal outline on the right; the renal area on the left side was indeterminate. An excretory urogram showed dilated tips of calices scattered over the large renal outline on the right, and the left kidney was indeterminate.

Cystoscopic examination was then conducted with the patient under anesthesia produced by intravenous injection of thiopental sodium. The bladder was found to be filled with dark red urine, but it appeared normal otherwise. Definite hemorrhagic spurts were seen issuing from the right orifice. A catheter was passed up the right ureter, and 35 cc. of dark red urine was aspirated from the renal pelvis. A retrograde pyelogram of the right side was made which showed the pelvis and calices to be dilated, grade 3, with multiple filling defects in the renal pelvis. Catheterization of the left ureter was not possible. Excretory urography was repeated, but ninety minutes after injection evidence of the contrast medium was not shown in the urogram in either renal area, and it was believed that the left kidney had little, if any, function remaining. For all practical purposes, therefore, the patient was considered to have a solitary kidney. A diagnosis was made of hydronephrosis complicated by a tumor of the renal pelvis. Exploration of the right kidney was advised.

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8. Ferris, D. O., and Daut, R. V.: Epithelioma of the Pelvis of a Solitary Kidney Treated by Electrocoagulation, J. Urol. **59**:577 (April) 1948.

At operation the kidney was exposed without difficulty through a primary posterolumbar incision. Hydronephrosis, grade 3, was present, and the kidney was enlarged to twice the normal size. The ureter was explored and found to be normal. A longitudinal incision was made in the posterior aspect of the renal pelvis, and a large organized clot of blood was removed. A papillary epithelioma was found which arose from the posterosuperior aspect of the renal pelvis and extended 1 cm. into the upper infundibulum. The greater portion of the tumor was excised along with a small segment at the site of origin. The pathologist reported this tumor to be a papillary squamous cell epithelioma, grade 2, without obvious infiltration of the renal pelvis. This being for all practical purposes a solitary kidney, it was not feasible to sacrifice any portion of it. It was decided, therefore, that the best method of destroying the lesion and still maintaining adequate renal function would be to electrocoagulate the remaining portion of the tumor thoroughly. This was carried out without difficulty. A nephrostomy tube was placed through the lower calyx, and the incision in the renal pelvis was closed. Fourteen days after operation the drainage was clear; an occasional erythrocyte was reported, and pyuria was graded 1. The patient continued to improve and was dismissed from the hospital on the twenty-eighth postoperative day. The nephrostomy tube was clamped, and he voided normally and without difficulty. After five days of normal micturition, the nephrostomy tube was removed, and the small defect where the tube had been located healed promptly. The concentration of urea was 64 mg. per hundred cubic centimeters of blood, and the carbon dioxide–combining power was 45.5 volumes per hundred cubic centimeters of plasma. An excretory urogram did not reveal any evidence of the medium or any renal outline on the left. On the right, dilated tips of the calices were seen scattered over the large right renal outline.

The patient was dismissed on the forty-ninth postoperative day in excellent condition. Correspondence eight months after operation revealed the patient to be in excellent health and completely free of symptoms.

Fagerstrom[9] discusses proliferative tumors of the ureter and the renal pelvis, with further observations on the significance of epithelial cell nests. He reports on 6 cases based on the histologic examination of 120 consecutive ureters removed at necropsy and the clinical history in

9. Fagerstrom, D. P.: Proliferative Tumors of the Ureter and Renal Pelvis, with Further Observations on the Significance of "Epithelial Cell Nests": Six Case Reports, J. Urol. **59**:333 (March) 1948.

2 cases of primary cancer of the ureter, 1 instance of benign tumor of the ureter, 2 epithelial growths of the renal pelvis and 1 case of ureteritis and pyelitis cystica. If urinary epithelium is stimulated to excessive activity, cellular proliferation may follow one or more of three courses: 1. There may be a general and widespread hyperplasia of the epithelium. 2. There may be an isolated, or focal, area of hyperplasia, resulting in a papillary excrescence above the surface level. 3. The focal proliferation may take a downward course beneath the epithelium, resulting in epithelial crypts and buds. Epithelium undergoing hyperplasia tends to become redundant, with the production of folds of mucosa. Sections through such tissue are apt to produce bizarre epithelial patterns, and unless the investigator is constantly conscious of the third dimension in the tissue block he quickly becomes disoriented and his deductions are in error.

Papillary new growths of the urinary epithelium are extremely rare when compared with the frequent incidence of epithelial buds. The forces governing the direction of growth are not clear, but it would seem that a mechanical factor may exert some influence. The flow of urine within the ureter creates a varying degree of hydrostatic pressure, which is intermittently augmented by contraction of the ureteral walls. Hyperplasia of the urinary epithelium may result from local irritation, such as chronic infection, or from noxious agents circulating in the fluids of the body. Epithelial buds and crypts are but bizarre expressions of epithelial hyperplasia. The theory of formation of cell nests proposed by von Brunn and accepted by most present day writers is not supported by this study. Cystic tumors of the ureteral epithelium derive from occluded mucosal crypts, whose lining cells exercise a latent secretory potentiality. Evidence has not been found that solid epithelial buds are directly associated with the origin of solid tumors of the urinary epithelium.

Hydronephrosis.—Stewart [10] describes a new operation used in treatment for hydronephrosis due to obstruction by a lower polar artery. The underlying principle of the operation is molding the kidney so that the lower polar or aberrant renal artery shall come into close relationship with the renal artery. In this position it no longer is capable of causing obstruction. The poles of the kidney are brought together as in the infant, but in order to maintain them in this new position, a second folding of the kidney is necessary so that the kidney approaches a ball in shape. The kidney is retained in this new shape by (1) a hoop

10. Stewart, H. H.: A New Operation for the Treatment of Hydronephrosis in Association with a Lower Polar (or Aberrant) Artery, Brit. J. Surg. **35**:51 (July) 1947.

of surgical gut tape, (2) sutures in the kidney tissue apposing the anterior surface of the poles and (3) overlapping and suture of the capsule which has been separated from the poles of the kidney. This operation has been performed in 18 cases in a period of ten years. In every case the patient is free from symptoms referable to the kidney and has sterile urine. In the majority of cases follow-up intravenous pyelograms showed satisfactory drainage of the pelvis and calices and good renal function. The configuration of the calices is altered as a result of the molding, and the lowest calyx occupies a position higher than the middle calyx. If the operation is performed in the way described, the new shape is permanent and the new look is that of a flower, the calices being the petals.

Cysts.—In certain instances of polycystic kidneys, the kidney may be only partially involved, suggesting a possible transition between diffusely polycystic kidneys and the lesions found in congenitally hypoplastic kidneys. Since only 4 cases of this type have been reported in the literature, Bayle and Gouygou [11] describe a case in detail. The patient, a man 36 years of age, was admitted to the hospital because of intermittent total anuria, although he had not suffered any pain. Hematuria had appeared fifteen days before his admission and recurred on exertion. His only other symptoms were a sensation of heaviness in the left lumbar region and constipation for about one and one-half months previous to admission. Routine urologic examination revealed only an enlarged left kidney. Intravenous urograms showed equal elimination from the two kidneys after five minutes, but the calices were not well defined. The left kidney was greatly enlarged, especially at the inferior pole. The conditions found suggested renal tumor or cyst of the inferior pole. Operation revealed a large left kidney, with its inferior pole greatly distended into a nonfluctuating irregular mass, adherent to the perineal tissues. The upper pole was normal. Extensive nephrectomy was followed by uneventful recovery. The cysts were confined entirely to the lower half of the kidney, with some islets of macroscopically intact parenchyma.

The cysts were of unequal size. The largest one was in the vicinity of the excretory duct and contained a yellowish fluid; some of the smaller cysts, rounded or deformed by pressure, contained a gelatinous substance of a reddish yellow color. Finally, scattered through the cortex, were small masses of microcysts a few millimeters in diameter, some almost invisible. The absence of muscle fiber and the presence of cortical cysts excluded the dysembryoplastic malformation of oligocystic,

11. Bayle, H. and Gouygou: Rein polykystique partiel: Rapp. et inform. A. franç. d'urol. **41**:263 (Oct. 7) 1947.

degenerative type described by Papin and Verliac, owing to faulty union between the two tubes of the nephron.

Stereoscopic and histologic studies showed the lesions to be those of true polycystic kidney, with only partial involvement of the kidney. In most cases diagnosis before operation is impossible, and only in the case reported by Ombredanne was the mass removed without performing nephrectomy.

These cysts are caused by obliteration of the nephron, but opinions are divided on the mechanism of obliteration. Thus Virchow attributes it to embryonic pyelitis, Rucker to a dominant congenital malformation and Brakeman to the unequal distribution of the epithelial and connective tissue elements of the kidney. Lambert demonstrated cysts communicating with the excretory ducts in all stages of the nephron. He also demonstrated a tissular activity in cystic nephrons. The right kidney in the case described by Bayle and Gouygou appeared completely normal. The future course in this case will be followed with interest to establish whether the condition is, or may become, bilateral.

Hypertension and Renal Disease.—Moore [12] reports the successful relief of hypertension of a girl 19 years old after removal of a kidney affected by arteriolar sclerosis. The blood pressure, which averaged 202 mm. of mercury systolic and 135 mm. diastolic, fell rapidly a few minutes after nephrectomy to 135 mm. systolic and 85 mm. diastolic and has remained in this range for three years. The remaining kidney was ectopic, with its lower pole in the pelvis. Moore recommended that physicians inform most of their patients of blood pressure findings in order to secure further knowledge of the duration of hypertension.

Hyperparathyroidism and Renal Complication.—Burns and Whitehead [13] discuss renal complications of hyperparathyroidism. Tumor of the parathyroid glands, a benign lesion, disturbs the body economy by causing the glands to produce an excessive amount of hormone leading to a pathologic condition called "primary hyperparathyroidism." The disease does not produce specific symptoms, and in the majority of cases it is unrecognized until complications, of which the most significant are skeletal changes and renal involvement, have developed. Hypercalcemia and hypophosphatemia are the most important laboratory findings. The only effective treatment is surgical removal of the adenoma. Complications referable to the urinary tract are treated according to present standard urologic procedures. Burns and Whitehead describe 4 cases to illustrate the various problems encountered in treatment.

12. Moore, J. G.: Hypertension Treated by Nephrectomy, J. Urol. **59**:297 (March) 1948.

13. Burns, E., and Whitehead, C. M.: Renal Complications of Hyperparathyroidism, J. Urol. **59**:664 (April) 1948.

Thrombosis.—Shea, Schwartz and Kobilak [14] report a case of hypertension in a 33 year old man due to partial occlusion of one renal artery, due to thrombosis, which was apparently cured by nephrectomy. They review briefly the literature on intrinsic occlusion of the renal artery associated with hypertension.

Infarction.—Regan and Crabtree [15] state that arterial, venous and traumatic infarctions of the kidney are diagnostic and surgical entities encountered with some frequency. An analysis of reported cases indicates certain characteristics of each form of infarction from which diagnosis may be made, if the condition is considered in the differential diagnosis. Sterile arterial infarction is the commonest of the three types. It seldom, if ever, requires surgical intervention. Operation is frequently performed for sterile infarction, through mistaken diagnosis. Septic arterial infarction is rare. An operative procedure is indicated. Chronic infarction tends to undergo cystic degeneration occasionally. Arterial infarction is closely associated with cardiac disease.

Venous infarction is a serious condition. Its close association in origin with septic states and the almost invariably infected clots make operation imperative when it is unilateral. Venous infarctions frequently, and arterial infarctions occasionally, are accompanied with large subcapsular or pararenal hematomas. Even in the absence of hematoma the kidney is enlarged.

Traumatic infarction is present in but a small portion of the reported cases. It is dependent on direct injury to the vessels. The most important single item in diagnosis of acute infarction of the kidney is complete, or almost complete, loss of function, irrespective of the degree of tissue involvement, in kidneys which remain unchanged in the pyelograms. Chronic infarction is recognizable in proportion to atrophy of the calices, which results from the scarring stage of infarction. Clinical studies of infarcted kidneys closely parallel the established experimental work.

Ormond,[16] in discussing Regan and Crabtree's paper, states that he reviewed 1,766 necropsies and renal infarcts were found in 95 instances, some of which were old healed infarcts and some of recent origin. The conditions most often responsible for the infarcts were in order of frequency, vegetative endocarditis, mural thrombi, general arterio-

14. Shea, J. D.; Schwartz, J. W., and Kobilak, R. E.: Thrombosis of the Left Renal Artery with Hypertension: Case Report, J. Urol. **59**:302 (March) 1948.

15. Regan, F. C., and Crabtree, E. G.: Renal Infarction: A Clinical and Possible Surgical Entity, J. Urol. **59**:981 (June) 1948.

16. Ormond, J. K., in discussion on Regan and Crabtree,[15] p. 1014.

sclerosis, peripheral thromboses and chronic nephritis. He reviewed the records of the patients for whom the diagnosis of renal infarct was recorded clinically in the twenty year period from 1926 to 1946. Renal infarct was reported in 52 cases, and a heart condition was responsible in 43 of them. The lesions found, in order of frequency, were rheumatic heart disease in 18 cases; hypertensive heart disease in 11 cases; bacterial endocarditis in 10 cases; arteriosclerotic heart disease in 8 cases, and coronary occlusion in 7 cases. Auricular fibrillation occurred in 15 cases and myocardial insufficiency in 14. In 9 instances in which a cardiac condition was not present the diagnoses were as follows: (1) hypertension, nephrosclerosis and syphilis; (2) hypertension and subarachnoid hemorrhage; (3) marked hypertension; (4) carcinoma of the liver; (5) carcinoma of the liver, diabetes and bronchopneumonia; (6) thrombophlebitis of a lower extremity; (7) septic thrombophlebitis of a lower extremity; (8) acute infectious arthritis of the knee and staphylococcic bacteremia; (9) streptococcic septicemia and tuberculous peritonitis. In this series 35 patients were males and 17 were females. Twenty-seven patients died while in the hospital; infarction occurred and the lesion was found at necropsy in 20 cases. Necropsy was not done in the other 7 cases.

Ormond also reviewed the records of patients who had renal infarcts and who were seen in the division of urology, usually in consultation, in a twenty year period. There were 10 such patients; 4 were examined cystoscopically and 1 by intravenous pyelography. Diagnosis of renal infarct was made in 8 of the 10 cases and was later confirmed at necropsy in 2 cases. The diagnosis was made at operation in 2. Venous infarcts are much rarer than the arterial variety. None was ever diagnosed clinically by Ormond, and necropsy revealed only 2 cases. In 1 of these direct extension was present from iliac veins to the vena cava to renal veins, and in the other thrombosis of the superficial veins in the inguinal region was present.

Regan and Crabtree give five points for the diagnosis of arterial infarction, the commonest form. The symptoms are those of an acute renal lesion such as stone, obstruction and infection, and we do not believe that complete urologic investigation is always or even usually indicated. In the presence of grave disease of the heart or blood vessels, that is, in four fifths of the cases, watchful waiting with a tentative diagnosis of infarct may be preferable to extensive manipulation, for neither the infarction nor the conditions with which it may be confused are likely to have immediate serious consequences in themselves. The underlying condition is the serious matter.

Hematoma.—Fort [17] reports a case of spontaneous perirenal hematoma caused by periarteritis nodosa. The patient, a Negro 39 years of age, was admitted because of jaundice, nausea and vomiting. Pronounced hypertension with advanced changes in the eyegrounds, jaundice and arteriosclerosis as well as chronic nephritis were present. On the fourteenth day in the hospital he suffered severe pain in the right portion of the abdomen, and shortly thereafter a mass developed. Pyelograms demonstrated the kidney and ureter on that side to be pushed anteriorly but not downward. Because of a persistent low grade elevation of temperature, it was thought that he had a perinephric abscess. Exploration of this area demonstrated a large hematoma which surrounded the kidney and which was removed intact. After a rather stormy postoperative course, the patient was discharged on the twenty-fifth postoperative day. The blood pressure was 150 mm. of mercury systolic and 110 mm. of mercury diastolic, and jaundice had disappeared. His condition was followed while he was in the outpatient department; the general condition grew progressively worse until he died of uremia a year after operation. His blood pressure at times was as high as 280 systolic and 120 diastolic. Eight days before his death the concentration of nonprotein nitrogen was 74 per cent.

Decapsulation.—Lowe [18] reports a case of chemical nephrosis caused by ingestion of oxalic acid in which the patient did not respond favorably to medical treatment and anuria, alarming edema and retention of nitrogen developed despite the intravenous administration of large amounts of fluids. Immediately after bilateral decapsulation, the kidneys began to function, secreting 1,240 cc. of urine in the first twenty-four hours after operation and 2,000 cc. in the second twenty-four hours. Urinary output was normal thereafter. The urine cleared after operation. The amount of albumin was reduced to a trace which persisted, and the number of red and white cells returned to normal. The edema disappeared. It is concluded that in this case the patient was relieved of his anuria by decapsulation of the kidneys, which indicates that the operation has merit in selected cases.

Shapiro [19] reports 2 cases in which anuria occurred after administration of sulfathiazole and in which the probable mechanism was the toxic action of the drug on the renal tubules. Bilateral decapsulation

17. Fort, C. A.: Spontaneous Perirenal Hematoma Secondary to Periarteritis Nodosa, J. Urol. **59**:307 (March) 1948.

18. Lowe E. S.: Renal Decapsulation in the Treatment of Oliguria and Anuria, U. S. Nav. M. Bull. **47**:959 (Nov.-Dec.) 1947.

19. Shapiro, I. J.: Decapsulation of the Kidney for Anuria Due to Sulfathiazole, J. Urol. **59**:538 (April) 1948.

was carried out in both cases, after which anuria ceased promptly, and ultimately both patients recovered completely. Early decapsulation is urged in similar cases because of the danger that irreversible changes in the kidney may occur if anuria persists too long.

ADRENAL GLAND

Neoplasm.—Goldner [20] reports a case of pheochromocytoma in a 20 year old girl having persistent decreased tolerance of carbohydrate after successful removal of the tumor. The prolonged hyperglycemia which was produced by the pheochromocytoma probably caused irreversible damage to the pancreatic islet cells. Except for diabetes the symptoms were rather mild. None of them alone would have been suggestive of the diagnosis, which proved to be correct at operation. This supports Howard's dictum that "when diabetes mellitus, hypertension and hypermetabolism are encountered the possibility of a pheochromocytoma should be considered."

Colston [21] reports 2 unusual cases of bilateral pheochromocytomas. In 1 case a pheochromocytoma had been removed four years previously at operation, but owing to technical difficulties it was necessary to leave behind a portion of the capsule. A recurrent tumor apparently developed from this portion of the capsule and was successfully removed at operation. The hypertensive crises, however, still persisted, with a positive reaction to a histamine test four months later. A second pheochromocytoma was exposed at operation on the opposite side and successfully removed. The patient's maternal aunt had been operated on nine years previously, and a pheochromocytoma, the entire adrenal gland and the left kidney were removed. She was relieved of symptoms for nine months, but the hypertensive crises recurred. A diagnosis of pheochromocytoma on the opposite side was made, and at operation a large tumor was exposed and successfully removed.

The technical difficulties at operation are discussed and the suggestion advanced that the exposure of both adrenal glands might be more satisfactorily carried out through an upper transverse abdominal incision. The advantages of such an approach are obvious, providing sufficient exposure can be obtained to remove a tumor if one should be encountered. This report is not intended to be a complete follow-up, but in the case mentioned the patient has been well for seventeen months and has not had further hypertensive crises and the result of the histamine test is negative; hence at the date of this review it

20. Goldner, M. G.: Pheochromocytoma with Diabetes: A Case Report and Discussion, J. Clin. Endocrinol. **7**:716 (Oct.) 1947.

21. Colston, J. A. C.: Surgical Aspects of Bilateral Familial Pheochromocytoma, J. Urol. **59**:1036 (June) 1948.

might be safely concluded that further excess of physiologically active chromaffin tissue is not present. In the second case the patient reports that she has been well in every respect and has not had a return of hypertensive crises for a period of sixteen months. The histamine test has not been repeated in this case, but the patient has recently been through a normal pregnancy, with delivery of a normal child, and reports that her blood pressure has never been above 115 mm. of mercury systolic and 80 mm. diastolic.

URETER

Anomaly.—Lange [22] describes a case of accessory ureter with an extravesical orifice in which the only symptom was escape of urine. The child was a girl 3 years of age when first examined, and at that time the source of the leakage could not be determined. Chromocystoscopic examination yielded negative results, as did intravenous pyelography. When seen again at the age of 6 years, the child, although obese, was in excellent general health, but, although bladder control was apparently perfect, the leakage continued. It was now discovered that the urine was trickling from the vagina, and the possibility of a supernumerary ureter with a vaginal orifice was considered. Excretory urograms as well as roentgenograms of the kidneys did not reveal any pathologic condition. Renal function was normal on both sides. Because of some slight irregularity in the pyelogram of the left kidney, it was assumed that an accessory ureter opening into the vagina must be present on that side. Operation confirmed this tentative diagnosis. The ureter was ligated, and the patient was cured of her incontinence. Every surgeon has his own technic for treatment of this anomaly, the simplest being ligature of the ureter. The three most important operations recommended are (1) heminephrectomy with ureterectomy, (2) total nephrectoureterectomy and (3) implantation of the ureter into the urinary bladder, the last being the most conservative. Implantation may be vaginal, abdominal intraperitoneal or abdominal extraperitoneal. The last facilitates control of infection in the cellular tissue. Prognosis is usually good, the primary operative mortality rate being only 1 per cent, with renal function usually preserved. Examination of the patient under discussion one and one-half years after operation did not show leakage of urine, but the left kidney was no longer functioning.

The case is reported to illustrate the difficulty of diagnosis of an accessory ureter with extravesical orifice in certain cases and the necessity for operation in some cases purely on the basis of the clinical findings.

22. Lange, G.: Ueber einen extravesikal mündenden akzessorischen Ureter und die klinischen Probleme dieser Missbildung, Ztschr. f. Urol. **40**:207 (Sept.-Oct.) 1947.

Differential diagnosis must be made from other conditions giving rise to incontinence, such as ureterovaginal fistula, vesicovaginal fistula and accessory urethra. In rare cases all urologic diagnostic methods yield only partial or equivocal results. Accessory ureter with extravesical orifice has been described as predisposing to renal tuberculosis and infection.

Neoplasm.—Presman and Ehrlich [23] state that true metastatic tumors of the ureter are rare. The diagnosis of metastatic tumor of the ureter has usually been made at postmortem examination or from a removed surgical specimen. The commonest sites of the primary lesion were the prostate and the stomach. In only 50 per cent of the cases did the primary lesion originate in a pelvic organ. Symptoms or signs due to ureteral involvement were present in 51 per cent of the patients. Pain in the back, increase of the blood urea or the nonprotein nitrogen, anuria and hematuria occurred in that order of frequency. In 90 per cent of the cases metastasis to other organs and structures of the body had occurred. All levels of the ureter were involved with equal frequency. Bilateral ureteral metastasis occurred in 60 per cent of the cases. The ureteral lesion was the diffuse, infiltrating type in 38 per cent of the cases, while in 62 per cent localized nodules were present. Partial or complete occlusion of the ureteral lumen was frequent and produced hydroureter or hydronephrosis in 70 per cent of the patients. Pyonephrosis was present in 8 cases, and ascending pyelonephritis occurred in 7 cases. Metastatic tumor of the ureter, although not a distinct clinical entity, should be considered in the differential diagnosis for patients with obstruction in the upper portion of the urinary tract. Presman and Ehrlich add 2 cases to the 34 previously reported.

Ectopic Ureter.—Meads [24] reports 2 cases of ectopic ureter. In 1 case the ureter opened into the vestibule, and in the other it opened into the upper portion of the vagina to the right of the cervix. Intravenous urograms failed to show an ectopic ureter in either case; neither did indigo carmine appear in the ectopic ureteral fluid. In 1 case a retrograde ureterogram of the ectopic ureter was finally obtained which determined the side of operation. In the second case a ureterogram could not be obtained, and so the side of operation had to be determined by deduction. Heminephrectomy and partial ureterectomy resulted in cure in each case.

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23. Presman, D., and Ehrlich, L.: Metastatic Tumors of the Ureter, J. Urol. **59**:312 (March) 1948.

24. Meads, A. M.: Ectopic Ureter, J. Urol. **59**:390 (March) 1948.

Physiology.—Lapides,[25] in discussing the physiology of the intact human ureter, states that tonus and rhythmic contraction of the intact human ureter are entirely independent of the central nervous system, including the autonomic nervous system and all its ganglions. The normal adequate stimulus for the initiation and maintenance of ureteral peristalsis is a stretching of the smooth muscle fibers of the ureter by the urine excreted from the kidney. Peristaltic activity of the ureter can be altered by changes in volume of urinary output, within certain limits. Rhythmic contractions and tonus of the intact human ureter were not directly affected by administration of tetraethylammonium chloride, procaine hydrochloride high spinal anesthesia, epinephrine and other drugs. Meperidine hydrochloride (demerol hydrochloride®), beta-hypophamine (pitressin®) and large doses of epinephrine decreased the secretion of urine. Neostigmine (prostigmine®) acted as a diuretic in half of the patients to whom it had been administered. No drug depressed ureteral peristalsis or decreased the tonus of the ureter. Morphine does not produce increased peristalsis and tonicity of the ureter.

Transplantation.—Cordonnier [26] discusses ureterosigmoid anastomosis, describing his method of mucosa to mucosa transplantation. This differs from the other methods in that the bowel is brought to the ureter rather than the ureter to the bowel, mucosa is transplanted to mucosa and the submucous tunnel is eliminated.

Preoperative care in preparation for this procedure is the same as for any other intestinal operation. The ureter is freed, and the stay suture from the underside of the ureter is attached to the sigmoid. The ureter is cut, and sutures are placed through the lumen of the ureter and the mucosa of the sigmoid. A second row of sutures is then taken from the adventitia of the ureter to the serosa of the sigmoid. The peritoneum is then sutured to the sigmoid.

This procedure has been followed by Cordonnier in 26 consecutive cases, without any deaths. Immediate postoperative complications have been absent. The author states that it is too early to evaluate the end results of this method, but he expresses the belief that they will prove satisfactory.

Trauma.—Moore [27] states that the principles governing the management of surgical injury of the ureter are determined to a great extent

25. Lapides, J.: The Physiology of the Intact Human Ureter, J. Urol. **59**:501 (April) 1948.

26. Cordonnier, J. J.: Ureterosigmoid Anastomosis, Surg., Gynec. & Obst. **88**:441 (April) 1949.

27. Moore, T. D.: The Management of the Surgically Traumatized Ureter, J. Urol. **59**:712 (April) 1948.

by their early or late discovery, the nature of the injury and the site. In instances of complete anuria after extensive pelvic operations, the possibility of bilateral occlusion of the ureters should be considered early rather than the adoption of treatment under the erroneous diagnosis of suppression of urine. In such cases deligation as employed in the past has been attended by a high mortality rate. It is believed, however, that the active cooperation of a cystoscopist when the abdomen is reopened would make the operation far safer than heretofore. Reimplantation of the ureter into the bladder may be considered preferable to ureteroureteral anastomosis. The latter often results in cicatricial stenosis at the site of anastomosis which makes it necessary for the patient to undergo numerous subsequent cystoscopic treatments and ureteral dilations. When a ureter has been severed or damaged, sacrifice of the involved kidney by ligation or nephrectomy is to be condemned except in most urgent circumstances. Transureteroureteral anastomosis may be considered along with ligation, nephrectomy, cutaneous ureterostomy and ureterointestinal anastomosis as a measure to be adopted when the ureter has been extensively damaged or severed at a high level. Of these procedures transureteroureteral anastomosis would appear the most desirable. Four cases are cited illustrative of various measures to be adopted in the conservative treatment of the surgically injured ureter. In all these both ureters were involved. Late follow-up findings are included, indicative of satisfactory functional results in all. No deaths occurred.

Obstruction.—According to Henline and Hawes,[28] the diagnosis of obstruction at the ureteropelvic junction is made by retrograde pyelograms with an added ten minute delayed roentgenogram. Most ureteropelvic obstructions result from narrowing of the lumen of the ureter even though aberrant vessels, bands and adhesions also may be present. Plastic operations should be performed only when sufficient renal tissue remains to sustain life. The Foley Y plastic operation has been more successfully performed by Henline and Hawes than other procedures but only when combined with nephrostomy drainage and the use of a splinting ureteral catheter for six weeks.

The operative mortality rate should compare favorably with that of other renal operations.

Renal calculi may form during prolonged nephrostomy drainage and, if discovered before the tube is removed, occasionally may be dissolved by irrigation. Subsequent nephrectomy became necessary in 2

28. Henline, R. B., and Hawes, C. J.: Ureteropelvic Obstructions: Symptoms and Treatment; Report of Seventy Cases, Sixty-Two Operations, J. A. M. A. **137**:777 (June 26) 1948.

cases. Results were poor in 10 per cent of the cases in which follow-up data could be secured. Satisfactory results, or improvement, were obtained in the remaining 90 per cent.

Ormond [29] reports 2 instances of ureteral compression which resulted from envelopment by a retroperitoneal, nonmalignant mass. In both instances there was sudden, complete anuria. This was preceded in both cases by ill health, unexplained anemia and backache. Urinary disturbance had not preceded it in either case. The microscopic appearance of retroperitoneal tissue in the 2 cases showed some similarity. In the second case the tissue was obviously inflammatory and of fairly recent origin. It is conceivable that the tissue in the first case represented a later stage of the process present in the second case. This also was in accord with the different periods during which the tissue in each case was observed. Ormond does not have theories to offer as to the genesis or development of these inflammatory masses or processes. It is possible that they have something to do with the lymph nodes of this region, but in neither case is there any history of preceding infection of the genital organs, legs or urinary tract or any evidence of diverticulitis of the bowel. The possibility of brucellosis has been suggested, but it was not suspected at the time and could not be proved now. Since the process is not invasive, its presence would be known only by the resulting compression of neighboring structures as it developed and spread and as they became enveloped by it. Of these structures the ureters would be most apt to give unmistakable evidence of compression. Both patients had severe backache, which may be attributable to the inflammatory process, but obscure backaches are common and rarely demand radical or emergency treatment, while complete obstruction of the ureters urgently demands attention.

Reconstruction.—Barnes and Farley [30] report the results of their work in the reconstruction of the lower segment of the ureter with a tube from a flap of bladder in 11 calves. The reconstructed ureter remained viable in all animals. Stricture at the site of anastomosis developed in 2, and urinary leakage at this point occurred in 3. These complications could probably have been avoided if proper technic had been used. In 5 good results were found at necropsy. The results of operations performed on this series of laboratory animals suggest that reconstruction of the lower segment of the ureter with a tube made

29. Ormond, J. K.: Bilateral Ureteral Obstruction Due to Envelopment and Compression by an Inflammatory Retroperitoneal Process, J. Urol. **59**:1072 (June) 1948.

30. Barnes, R. W., and Farley, S.: Reconstruction of Lower Segment of Ureter with Tube Made from Bladder Flap: Preliminary Report, J. Urol. **59**:466 (March) 1948.

from a flap of bladder is indicated in patients whose ureters have been injured to such an extent that reanastomosis or reimplantation into the bladder is impossible.

TESTIS

Neoplasm.—In a series of 250 tumors of the testis Lewis [31] found that 43 had metastasized at the time of the patient's admisison. One hundred and sixty-nine patients underwent radical orchiectomy. Of these patients, 24 per cent have died. Eighty-one patients either had inoperable metastatic processes on admission or underwent simple orchiectomy and irradiation because of the diagnosis of seminoma. Thirty-two per cent of the total series have died, 8 patients having died from perforation of the stomach or bowel due to excessive irradiation. At necropsy no tumor was found. It is interesting to note that, except in the case of chorioepithelioma, the rate of metastasis was higher than the mortality rate, which indicated that treatment by radiation and operation was thorough.

For benign interstitial cell tumors, simple orchiectomy is probably sufficient. For teratomas, radical orchiectomy is indicated without radiation therapy. For seminoma, simple orchiectomy plus radiation therapy is probably sufficient. Lewis recommends 1,000 r as a prophylactic dose to the entire retroperitoneal lymph drainage area. Radical orchiectomy may not be indicated for treatment of seminoma, but the information gained by retroperitoneal dissection aids the roentgenologist in planning treatment. For undifferentiated carcinoma, adenocarcinoma and papillary adenocarcinoma, radical orchiectomy is indicated, followed by prophylactic roentgen therapy in dosage not to exceed 3,000 r. For trophoblastic tumors, choriocarcinoma and chorioepithelioma, radical orchiectomy is indicated; radiation therapy in dosage of 5,000 r should not be used except when inoperable metastatic nodes remain. For teratoma with malignant embryonic elements, irradiation is indicated only when inoperable metastatic nodes are found.

Meltzer and Bloom [32] report the successful removal of a highly malignant adenocarcinoma of the right testis of an 8 month old boy, with an apparent cure at the end of six years. The tumor, which weighed 49 Gm., was removed by ligation and transection of the spermatic cord at the level of the external inguinal ring. Radiation therapy was not given. It is believed this is the only reported five year survival.

31. Lewis, L. C.: Testis Tumors: Report on Two Hundred and Fifty Cases, J. Urol. **59**:763 (April) 1948.

32. Meltzer, A., and Bloom, B.: Malignant Testicular Neoplasms in Infancy: Report of a Case with a Six-Year Survival, New England J. Med. **237**:513 (Oct. 2) 1947.

SEMINAL VESICLE

Neoplasm.—McCrea [33] states that primary carcinoma of the seminal vesicles is rare but not as rare as the sparsity of literature on the subject would suggest. To date 23 cases have been reported in the literature, and McCrea adds 1 case. In only 10 of these cases has the disease been proved histologically. The cardinal symptoms of primary carcinoma of the seminal vesicles are frequency, difficulty of urination and hematuria associated with the rectal mass palpable above the prostate. It may be difficult to distinguish primary carcinoma of the seminal vesicles from primary carcinoma of the rectum and from Blumer's shelf tumors; biopsy is the best method. The treatment of primary carcinoma of the seminal vesicles is unsatisfactory. Excision is impossible, and only palliative measures may be considered.

(To Be Continued)

33. McCrea, L. E.: Primary Carcinoma of the Seminal Vesicles: Differentiation from Extrarectal and Rectal Carcinoma and Comparative Study, J. A. M. A. **136**:679 (March 6) 1948.

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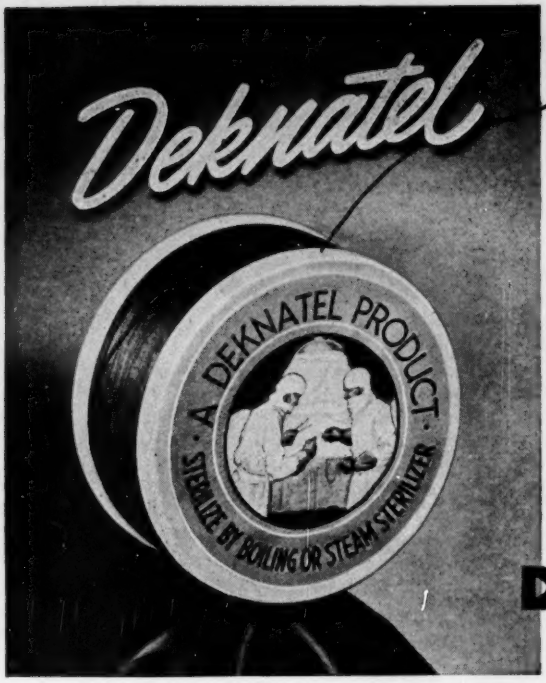

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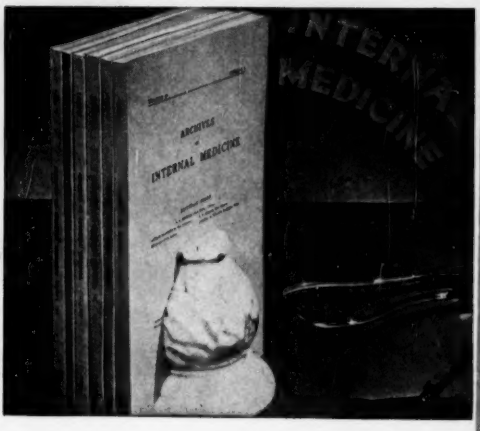

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